Total Synthesis of Aflastatin A

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A dissertation presented

by

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Total Synthesis of Aflastatin A

Abstract

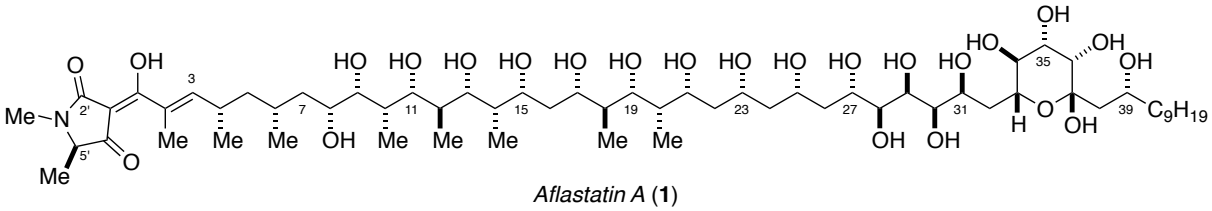
The syntheses of aflastatin A (**1**) and its C3–C48 degradation fragment (**2**) are described. The syntheses feature several complex diastereoselective fragment couplings, including a C35–C36 anti-Felkin-selective boron-mediated oxygenated aldol reaction, a C15–C16 Felkin-selective trityl-catalyzed Mukaiyama aldol reaction, and a C26–C27 chelate-controlled aldol reaction involving soft enolization with magnesium.

Careful comparison of the spectroscopic data for the synthetic aflastatin A C3–C48 degradation fragment (**2**) to that reported by the isolation group revealed a structural misassignment in the lactol region of the naturally derived degradation product. The cause of the mismatch was initially believed to be stereochemical in origin. Ultimately, the data reported for the naturally derived aflastatin A C3–C48 degradation lactol (**2**, R = H) was attributed to its derivative lactol trideuteriomethyl ether ($R = CD_3$).

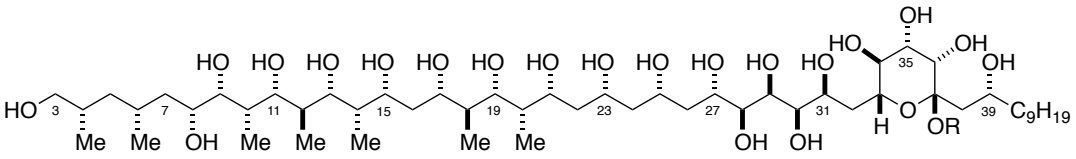
Further, the absolute configurations of six stereogenic centers (C8, C9 and C28–C31) in aflastatin A (**1**) were formally revised by the isolation group prior to completion of its total synthesis. The synthesis of the aflastatin A C3–C48 lactol trideuteriomethyl ether and its spectroscopic match to the naturally derived C3–C48 degradation fragment confirm the stereochemical revision.

The synthesis of a degradation product containing the tetramic acid and two overlapping stereocenters (C4 and C6) was also achieved. Its spectroscopic match to the corresponding naturally derived degradation fragment verified the absolute configuration of

the aflastatin A C5' stereocenter. When combined with previous degradation fragment syntheses, and eventually the total synthesis of aflastatin A, the revised stereochemical assignment of aflastatin A was fully affirmed.



Aflastatin A (**1**)



Aflastatin A C3–C48 Degradation Fragment (**2**, R = H)

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Acknowledgments

First and foremost, I would like to thank my research advisor, Prof. David A. Evans, for accepting me into his research group, providing intellectual and financial support, and most importantly, showing a great amount of patience. I think we both knew we were in for the long haul when he referred to my work on the aflastatin project as occurring on a geological timescale (lab members affectionately call this "Beiger time"). I hope you understand that I needed this time to make sure we got our work done to the best of our ability. I believe I speak for every member of the aflastatin project in saying that it has been a true privilege to work not only within this group, but on a molecule that stands to be the last polyketide natural product completed by this laboratory. I can only hope that it provides a satisfactory final chapter to the rich aldol legacy that you and this group will leave behind.

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Bill Trenkle, Jing Zhang, Jason Burch, David Thaisrivongs, Victor Cee and Sarah Siska.

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To Mom, Dad and Justin.

"We few, we happy few, we band of brothers."

– *Henry V*, William Shakespeare

Å	angstrom
Ac	acetyl
aq	aqueous
AsA	aflastatin A
9-BBN	9-borabicyclo[3.3.1]nonane
BcA	blasticidin A
BINAP	2,2'-bis(diphenylphosphino)-1,1'-dinaphthyl
Bn	benzyl
BOM	benzyloxymethyl
box	bisoxazoline
Bu	butyl
Bz	benzoyl
calcd	calculated
cat	catalytic
Cbz	benzyloxycarbonyl
cm^{-1}	wavenumber(s)
CSA	camphor sulfonic acid
cod	1,5-cyclooctadiene
COSY	correlation spectroscopy
Cy	cyclohexyl
δ	chemical shift
d	day(s)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBALH	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
E	entgegen (German)
ee	enantiomeric excess

ent	enantiomeric
epi	epimeric
eq	equation
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
g	gram(s)
h	hour(s)
HMPA	hexamethylphosphoramide
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HPLC	high-pressure liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
IBX	*ortho*-iodoxybenzoic acid
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
L	liter(s), or ligand
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
2,6-lut.	2,6-lutidine (2,6-dimethylpyridine)
M	molar, or metal
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOP	2-methoxypropan-2-yl
MS	molecular sieves

MTPA	α-methoxy-α-(trifluoromethyl)phenylacetyl
m/*z*	mass-to-charge ratio
n	normal
NaHMDS	sodium bis(trimethylsilyl)amide
NOE	nuclear Overhauser effect
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
Piv	pivaloyl (trimethylacetyl)
PMB	*para*-methoxybenzyl
PMP	1,2,2,6,6-pentamethylpiperidine
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
p-TsOH	*para*-toluenesulfonic acid (monohydrate)
py	pyridine
quant.	quantitative
quinox	2-(4,5-dihydro-2-oxazolyl)quinoline
R	alkyl group (generic)
Ref.	reference
ROE	rotating frame Overhauser effect
rt	room temperature
sat.	saturated
SM	starting material
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t or *tert*	tertiary
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl

TMS	trimethylsilyl
TOF	time-of-flight
TPS	triphenylsilyl
Tr	trityl
TS	transition state
v/v	volume per unit volume
wt%	weight percent
Z	zusammen (German)
)))	sonication

Chapter

1

Introduction to Aflastatin A

I. Aflatoxins

The aflatoxins represent a group of mycotoxins produced by fungi of the *Aspergillus* genus (Figure 1.1).[1] Aflatoxins produced by strains of *A. flavus* and *A. parasiticus* regularly contaminate food and feedstock derived from infected corn, cotton, grain and peanut crops.[2] Contamination of agricultural commodities is problematic because aflatoxins exhibit potent toxicity and carcinogenicity in mammals.[3] Limiting the amount of aflatoxin that enters our food supply is important for protecting human and animal health while minimizing economic loss.[4] As an example, aflatoxin levels are regulated within the United States by the Food and Drug Administration (FDA), and must not exceed 20 parts-per-billion in food destined for

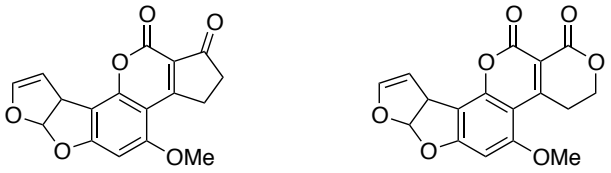
(1) Goldblatt, L., Ed. *Aflatoxin, Scientific Background, Control, and Implications*; Academic Press, New York, NY, 1969.

(2) (a) Detroy, R.W.; Lillehoj, E.B.; Ciegler, A. Aflatoxin and Related Compounds. In *Microbial Toxins: Fungal Toxins*; Ciegler, A., Kadis, S., Ajl, S.J., Eds.; Academic Press: New York, 1971; Vol. 6, pp 3–178; (b) Diener, U.L.; Cole, R.J.; Sanders, T.H.; Payne, G.A.; Lee, L.S.; Klich, M.A. *Annu. Rev. Phytopathol.* **1987**, *25*, 249–270.

(3) (a) Squire, R.A. *Science* **1981**, *214*, 877–880; (b) Eaton, D.L., Groopman, J.D., Eds.; *The Toxicology of Aflatoxins: Human Health, Veterinary, and Agricultural Significance*; Academic Press: San Diego, CA, 1994; (c) Newberne, P.M.; Butler, W.H. *Cancer Res.* **1969**, *29*, 236–250.

(4) (a) Payne, G.A. Process of Contamination by Aflatoxin-Producing Fungi and Their Impact on Crops. In *Mycotoxins in Agriculture and Food Safety*; Sinha, K.K., Bhatnagar, D., Eds.; Marcel Dekker: New York, 1998; pp 279–306. (b) Bennett, J.W.; Klich, M. *Clin. Microbiol. Rev.* **2003**, *16*, 497–516.

human consumption.[5]



Aflatoxin B_1 *Aflatoxin G_1*

Figure 1.1. Representative aflatoxins.

Few methods exist for protecting agricultural products from aflatoxin contamination. Traditionally, fungicides have been used to control the propagation of aflatoxigenic fungi, but they are often toxic to mammals, and provoke the emergence and pervasion of resistant strains. More recently, non-aflatoxigenic strains of *A. flavus* were developed to displace aflatoxin-producing strains from crop fields, but application timing, cost, and overall effectiveness of this technology are limiting.[6]

Alternatively, specific inhibitors of aflatoxin biosynthesis that lack fungicidal activity are desirable.[7] Since aflatoxins do not appear to be essential for fungal growth and viability, it should be possible to inhibit their synthesis without selecting for resistant strains. Aflatoxin production inhibitors should also provide new insight into the mechanism and regulation of aflatoxin biosynthesis by fungi on the molecular level. Study in this area should aid the development of more effective and economically practical means of minimizing aflatoxin contamination.

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(5) U.S. Food and Drug Administration. Action Levels for Aflatoxins in Animal Feeds. *Compliance Policy Guide*, Sec. 683.100, 1979 (revised 1994).

(6) (a) Dorner, J.W.; Lamb, M.C. *Mycotoxin Res*. **2006**, *22*, 33–38; (b) Cotty, P.J. *Phytopathology* **1994**, *84*, 1270–1277.

(7) (a) Zaika, L.L.; Buchanan, R.L. *J. Food Prot*. **1987**, *50*, 691–708; (b) Wheeler, M.H.; Bhatnagar, D. *Pestic. Biochem. Physiol*. **1995**, *52*, 109–115; (c) Wheeler, M.H.; Bhatnagar, D.; Rojas, M.G. *Pestic. Biochem. Physiol*. **1989**, *35*, 315–320; (d) Dutton, M.F.; Anderson, M.S. *J. Food Prot*. **1980**, *43*, 381–384.

II. Isolation and Biological Activity

Aflastatin A (AsA, **1**) was discovered during a screen of microbial metabolites that specifically targeted aflatoxin production in *A. parasiticus* (Figure 1.2).[8] AsA was isolated by Sakuda and coworkers from the mycelial extract of the bacterium *Streptomyces* sp. MRI142, which in turn was isolated from a soil sample collected in Zushi-shi, Kanagawa prefecture, Japan. Similarly, blasticidin A (BcA, **2**) was isolated by Fukunaga, Yonehara and their respective coworkers from the soil bacterium *Streptomyces griseochromogenes*.[9] BcA was initially reported to show antifungal activity towards the rice blast pathogen *Pyricularia oryzae*. Later, Sakuda and coworkers reevaluated BcA as an inhibitor of aflatoxin production after noticing homologous physicochemical properties between it and AsA.[10]

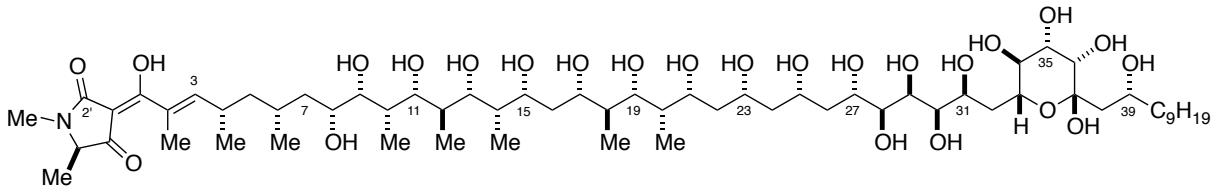


Figure 1.2. Structures of aflastatin A (**1**) and blasticidin A (**2**).

(8) (a) Sakuda, S.; Ono, M.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Am. Chem. Soc.* **1996**, *118*, 7855–7856; (b) Ono, M.; Sakuda, S.; Suzuki, A.; Isogai, A. *J. Antibiotics* **1997**, *50*, 111–118; (c) Ono, M.; Suzuki, A.; Isogai, A.; Sakuda, S. Production Aflastatin A from *Streptomyces* sp., A Pharmaceutical Composition and Methods of Use. U.S. Patent 5,773,263, June 30, 1998.

(9) (a) Fukunaga, K.; Misato, T.; Ishii, I.; Asakawa, M. *Bull. Agric. Chem. Soc. Jpn.* **1955**, *19*, 181–188; (b) Kōno, Y.; Takeuchi, S.; Yonehara, H. *J. Antibiotics* **1968**, *21*, 433–438.

(10) (a) Sakuda, S.; Ono, M.; Ikeda, H.; Inagaki, Y.; Nakayama, J.; Suzuki, A.; Isogai, A. *Tetrahedron Lett.* **1997**, *38*, 7399–7402; (b) Sakuda, S.; Ono, M.; Ikeda, H.; Nakamura, T.; Inagaki, Y.; Kawachi, R.; Nakayama, J.; Suzuki, A.; Isogai, A.; Nagasawa, H. *J. Antibiotics* **2000**, *53*, 1265–1271. (c) Ono, M.; Suzuki, A.; Isogai, A.; Sakuda, S. Aflatoxin Contamination Inhibitor and Aflatoxin Contamination-Inhibiting Method. U.S. Patent 6,121,310, September 19, 2000.

Owing to their similar chemical properties, AsA and BcA exhibit comparable biological activities.[11] AsA and BcA inhibit production of both aflatoxin B and G groups by *A. parasiticus* (IC_{50} = 0.07 and 0.04 μM, respectively) without significantly affecting fungal growth. They also reduce production of the pentaketide-derived melanin in the fungus *Colletotrichum lagenarium*.[12] Biological assays reveal that AsA and BcA suppress the expression of enzymes (i.e. PKS1) and a regulatory protein (AflR) involved in early steps of the biosyntheses of aflatoxin and melanin,[13] but exact molecular targets for these natural products have yet to be identified. Collectively, AsA and BcA exhibit antibiotic activity against various fungi, bacteria and yeast. Independently, AsA inhibits propagation of subcutaneously transplanted mouse adenocarcinoma,[8c] whereas BcA suppresses ribosomal protein synthesis in the yeast *Saccharomyces cerevisiae*.[14]

III. Structure Elucidation

Aflastatin A is a 3-acyltetramic acid natural product that bears a highly oxygenated and long alkyl chain.[8a] It contains 29 stereogenic centers, one stereodefined (*E*) alkene (C2–C3), a six-membered lactol (C33–C37), and is capped by a D-alanine-based tetramic acid moiety (N1'–C6') that is subject to both rotameric and tautomeric equilibria. As a polyketide, AsA bears hydroxyl groups at several unexpected positions (C8, C28, C30, C34, and C36), but this unusual oxidation pattern can be explained by the incorporation of five glycolic acid

(11) Sakuda, S. *Mycotoxins* **2010**, *60*, 79–86.

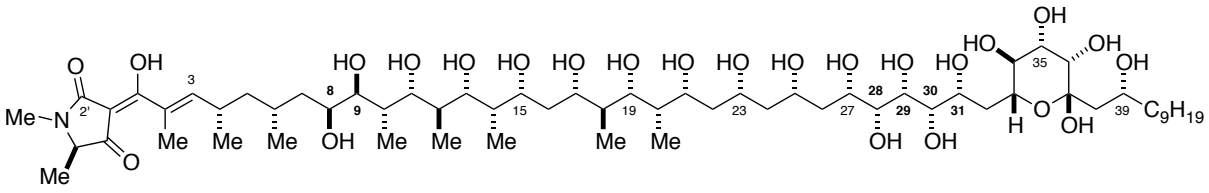
(12) Okamoto, S.; Sakurada, M.; Kubo, Y.; Tsuji, G.; Fujii, I.; Ebizuka, Y.; Ono, M.; Nagasawa, H.; Sakuda, S. *Microbiology* **2001**, *147*, 2623–2628.

(13) (a) Kondo, T.; Sakurada, M.; Okamoto, S.; Ono, M.; Tsukigi, H.; Suzuki, A.; Nagasawa, H.; Sakuda, S. *J. Antibiotics* **2001**, *54*, 650–657; (b) Sakuda, S. *Mycotoxins* **2002**, *52*, 153–159; (c) Sakuda, S.; Kondo, T.; Yoshinari, T.; Nagasawa, H. *Mycotoxins* **2003**, *Suppl. 3*, 99–105; (d) Yoshinari, T.; Akiyama, T.; Nakamura, K.; Kondo, T.; Takahashi, Y.; Muraoka, Y.; Nonomura, Y.; Nagasawa, H.; Sakuda, S. *Microbiology* **2007**, *153*, 2774–2780.

(14) Yoshinari, T.; Noda, Y.; Yoda, K.; Sezaki, H.; Nagasawa, H.; Sakuda, S. *J. Antibiotics* **2010**, *63*, 309–314.

subunits during its biosynthesis.[15]

Sakuda and coworkers first reported preliminary structural information for AsA in concert with its isolation.[8a] They used a combination of spectroscopic and degradation experiments to elucidate its molecular formula, structural connectivity, and relative stereochemistry in the C33–C37 lactol region. The same group later assigned the complete relative and absolute stereochemistry of AsA as represented by structure **3** (Figure 1.3).[16] They ultimately corrected the configuration of six stereogenic centers (C8, C9 and C28–C31), which will be discussed in due course.



3

Figure 1.3. Initial structural assignment of aflastatin A (AsA).

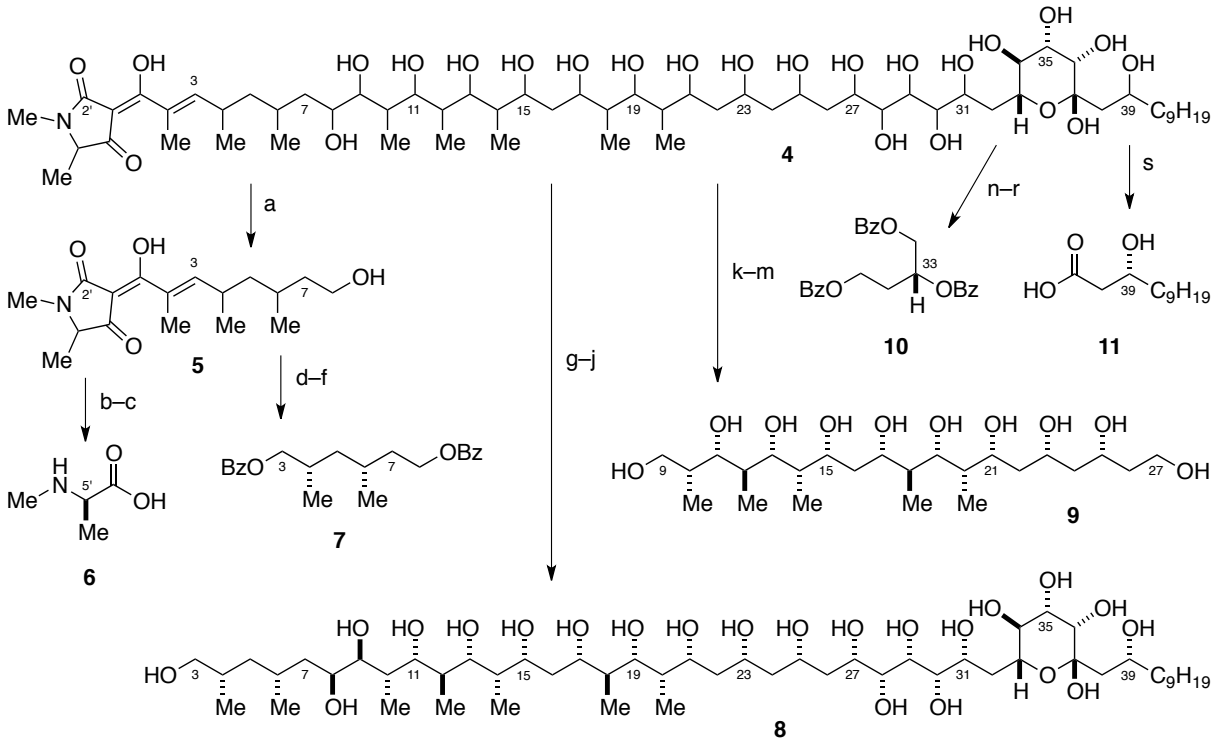
The initial stereochemical assignment of AsA (**3**) relied upon its chemical degradation and spectroscopic analyses of the resultant fragments (Scheme 1.1). The absolute configurations of the smallest degradation fragments were determined as follows: *N*-methyl-D-alanine (**6**) by Marfey's method, β-hydroxyacid **11** by comparison of its optical rotation data to literature value, and both dibenzoate **7** and tribenzoate **10** by comparison of their respective circular dichroism spectra and optical rotation values to data obtained from authentic samples. The relative stereochemistry of the C9–C27 and C3–C48 degradation

(15) Ono, M.; Sakuda, S.; Ikeda, H.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Antibiotics* **1998**, *51*, 1019–1028.

(16) Ikeda, H.; Matsumori, N.; Ono, M.; Suzuki, A.; Isogai, A.; Nagasawa, H.; Sakuda, S. *J. Org. Chem.* **2000**, *65*, 438–444.

fragments **9** and **8**, respectively, was elucidated by *J*-based configuration analysis[17] and partly supplemented with ROE correlation data. The absolute and relative configurations of the degradation fragments were then connected to provide a complete stereochemical depiction of AsA.

Scheme 1.1. Degradation of aflastatin A (**4**).



Reagents and conditions: (a) $NaIO_4$; $NaBH_4$; (b) $NaIO_4$; (c) HCl (aq.); (d) O_3; Me_2S; (e) $LiAlH_4$; (f) BzCN, nBu_3N; (g) HCl, MeOH; (h) O_3; $NaBH_4$; (i) Ac_2O, py, DMAP; (j) NaOMe; Dowex-50W (H^+); (k) $NaIO_4$; $NaBH_4$; (l) Ac_2O, py, DMAP; (m) NaOMe; (n) HCl, MeOH; (o) $NaIO_4$; (p) $NaBH_4$; (q) HCl (aq.); (r) BzCl, py, DMAP; (s) $NaIO_4$.

The relative stereochemistry of C9–C27 degradation fragment **9** was reinforced by [^{13}C]acetonide analysis,[18] and its absolute configuration elucidated by Mosher ester analysis[19] (Scheme 1.2).[20] First, pentaacetonide **12** and tetraacetonide **14** were synthesized and analyzed

(17) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866–876.

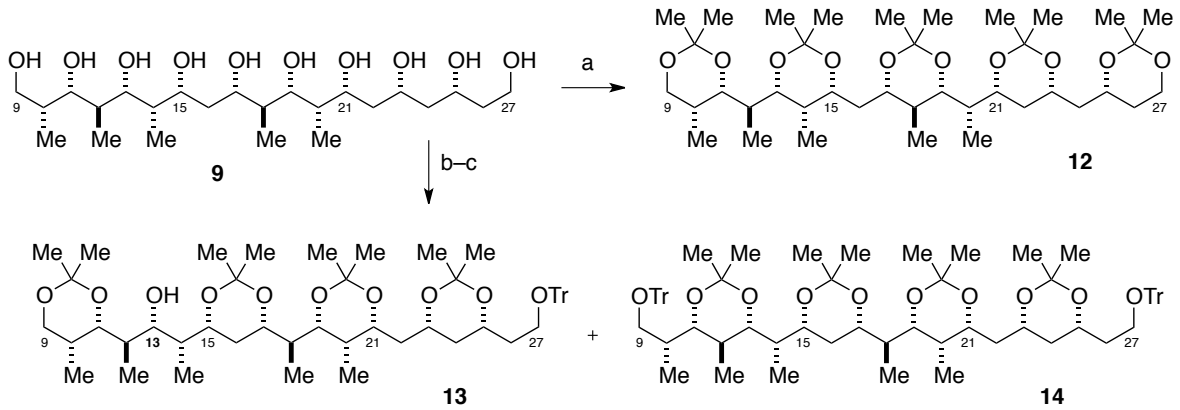
(18) Rychnovsky, S.D.; Rogers, B.N.; Richardson, T.I. *Acc. Chem. Res.* **1998**, *31*, 9–17.

(19) Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.

(20) Sakuda, S.; Ikeda, H.; Nakamura, T.; Nagasawa, H. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 407–412.

to establish 1,3-syn diol relationships across the entire C9–C27 region. Second, the MTPA esters of carbinol **13** were prepared to determine the absolute configuration at C13. Taken together, these derivations provided additional support for the initial absolute configuration assignment of C3–C48 degradation fragment **8**, and therefore AsA.

Scheme 1.2. Derivitization of AsA C9–C27 degradation fragment **9**.



Reagents and conditions: (a) 2,2-dimethoxypropane, CSA, acetone, rt; Et_3N; (b) TrCl, py, DMAP, MeCN, rt; (c) $Me_2C(OMe)_2$, *p*-TsOH, DMF, rt; Et_3N.

IV. Stereochemical Revision

Aflastatin A attracted the attention of the Kishi group during their development of a universal NMR database as a tool for the stereochemical assignment of acyclic regions of natural products.[21] The structural array of contiguous carbinols seen in the C27–C31 region of AsA was particularly suited for comparison with their library of 1,2,3,4,5-pentaols. Kishi and coworkers observed that each pentaol diastereomer exhibited a distinct spectroscopic profile. Specifically, comparison of their spin-coupling profiles to the reported data (Figure 1.4A) compelled them to suggest that the relative stereochemistry in the C27–C31 pentaol region of AsA degradation fragment **8** be revised from syn/syn/syn/syn (Figure 1.4B) to anti/syn/syn/syn (Figure 1.4C).

(21) (a) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562–2571; (b) Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379–14393.

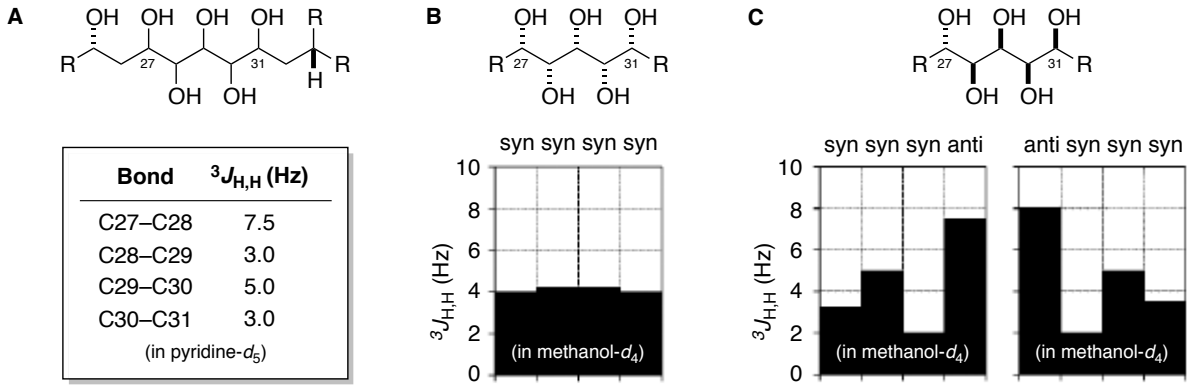
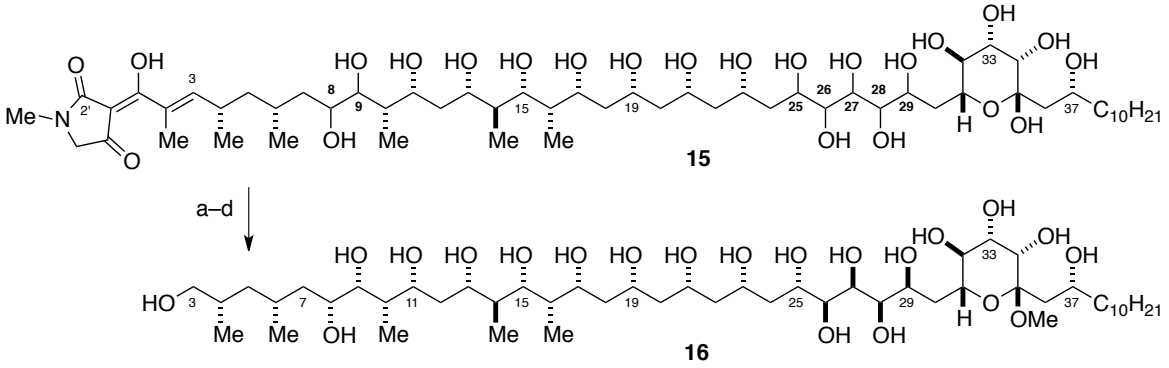


Figure 1.4. Spin-coupling constant comparison of the C27–C31 pentaol region of AsA degradation fragment **8** (A) to Kishi's database pentaols (B,C).

Somewhat concurrently, Sakuda and coworkers deciphered the structure of blasticidin A (BcA).[22] As with AsA, they used a combination of spectroscopic and degradation experiments to elucidate its relative and absolute stereochemistry. Unlike AsA, however, they took greater caution in assigning stereochemistry to the C8–C9 diol and C25–C29 pentaol regions, as purposefully left ambiguous in structure **15** (Scheme 1.3).

Scheme 1.3. Degradation of blasticidin A (**15**) to C3–C47 fragment **16**.



Reagents and conditions: (a) HCl, MeOH; (b) O_3; $NaBH_4$; (c) Ac_2O, py, DMAP; (d) NaOMe; Dowex-50W (H^+).

Sakuda and coworkers relied on BcA C3–C47 degradation fragment **16** to determine

(22) Sakuda, S.; Ikeda, H.; Nakamura, T.; Kawachi, R.; Kondo, T.; Ono, M.; Sakurada, M.; Inagaki, H.; Ito, R.; Nagasawa, H. *J. Antibiotics* **2000**, *53*, 1378–1384.

the absolute configuration of these positions.[23] They used *J*-based configuration analysis[17] in combination with the NMR database method[21] to assign the relative configurations from C23–C25 as syn, and C25–C29 as anti/syn/syn/syn. Less expected was that they assigned the absolute configurations of C8 and C9 to be opposite those proposed for AsA. During their analysis, they discovered that in the C8–C9 diol region, the spin-coupling profile of BcA degradation fragment **16** (Figure 1.5A) was very similar to that of AsA fragment **8**. Such spectral similarity allowed them to correct a coupling constant value ($^3J_{H\text{-}9,H\text{-}10}$) attributed previously to AsA fragment **8** (Figure 1.5B), and prompted them to revise their previous assignments for C8 and C9 in AsA. Ultimately, Sakuda and coworkers revised the configuration of six stereogenic centers (C8, C9 and C28–C31) in AsA to match the corresponding stereocenters in BcA.

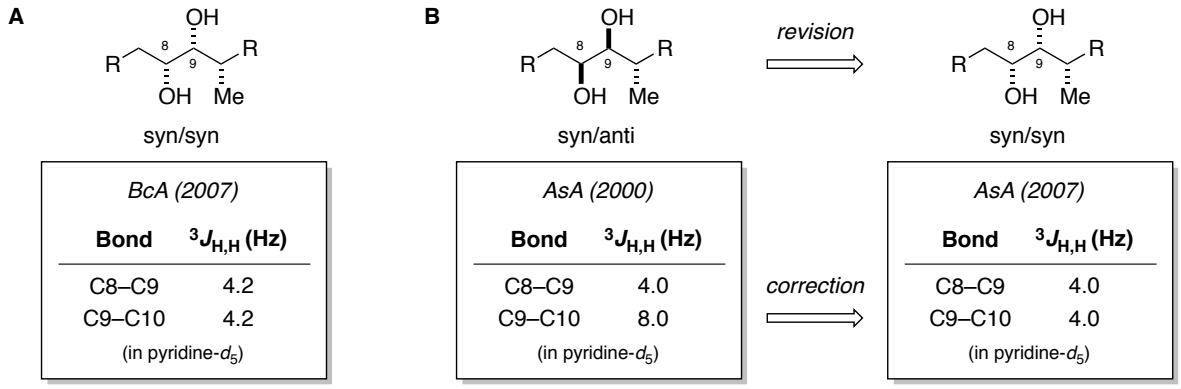


Figure 1.5. Stereochemical assignment of the C8–C9 diol region of BcA degradation fragment **16** (A) and revision of AsA fragment **8** (B).

To support their assignment of the C8–C11 region of BcA (and reassignment of AsA), Sakuda and coworkers synthesized four model diastereomers **17a–d** (Figure 1.6A).[23] Among the models, only the coupling constant values observed for syn/syn diastereomer **17a** and the C8–C10 region of BcA degradation fragment **16** were comparable.

(23) (a) Sakuda, S.; Matsumori, N.; Furihata, K.; Nagasawa, H. *Tetrahedron Lett*. **2007**, *48*, 2527–2531; (b) Sakuda, S.; Yoshinari, T.; Nakamura, K.; Akiyama, T.; Takahashi, Y.; Muraoka, Y.; Nonomura, Y.; Nagasawa, H. *Mycotoxins* **2006**, *Suppl. 4*, 135–140.

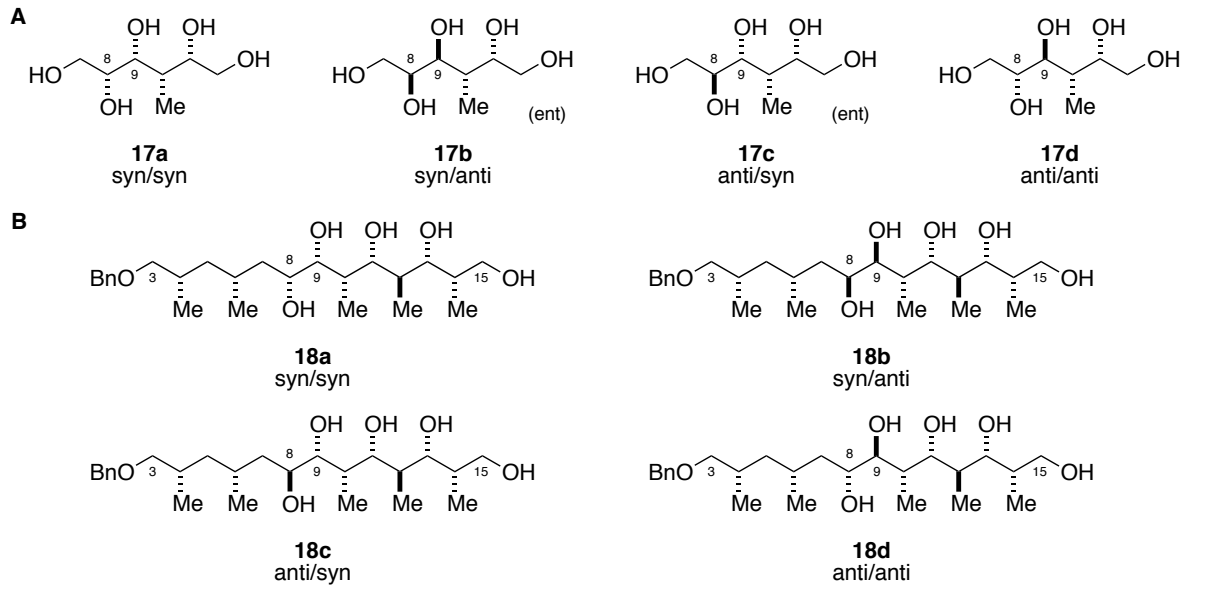


Figure 1.6. Sakuda's (A) and Evans' (B) models for the C8–C9 diol region of AsA and BcA.

Nevertheless, the NMR databases suggest that interactions between structural motifs that are two (but potentially four) carbons away are significant.[21] Because our group had been actively pursuing the synthesis of AsA since its initial stereochemical assignment, we desired stronger evidence for the reassignment of C8 and C9 and synthesized the corresponding C3–C15 model diastereomers **18a–d** (Figure 1.6B).[24] The syn/syn diastereomer (**18a**) provided not only the closest spectral match, but also assurance that redirecting future synthesis efforts toward revised structures **1** and **19** was appropriate (Figure 1.7).

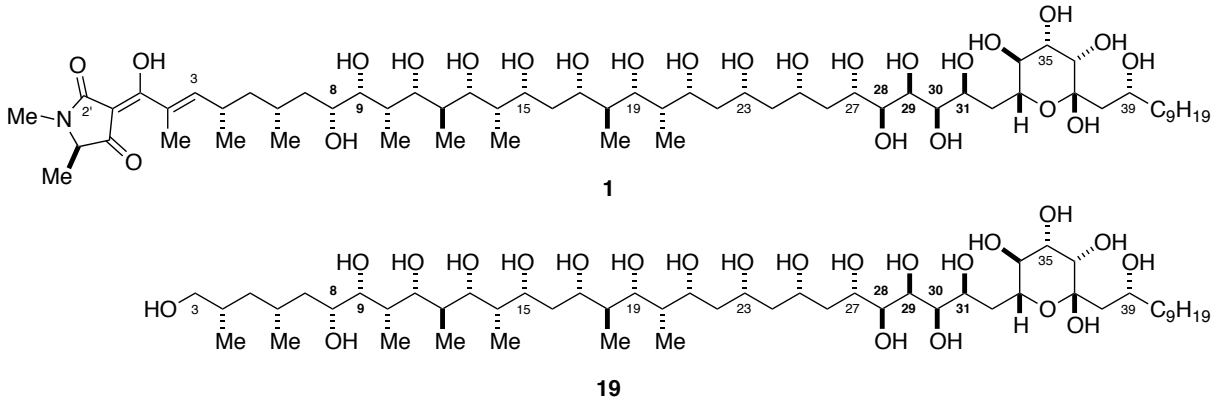


Figure 1.7. Revised structural assignment of AsA (**1**) and C3–C48 degradation fragment **19**.

(24) Young, J.M. *Studies Toward the Synthesis of Aflastatin A*. Ph.D. Thesis, Harvard University, **2008**.

V. Synthesis Achievements Made Prior to the Stereochemical Revision

The Evans group has a long-standing interest in the use of aldol reactions for the construction of polyacetate and polypropionate natural products. We selected aflastatin A (**3**) as a synthesis target due to the challenges posed by its densely oxygenated structure. We were attracted by the opportunity to develop aldol chemistry for the construction of natural products containing contiguous polyols. Despite uncertainty surrounding the initial stereochemical assignment, our laboratory made enduring advances toward the synthesis of AsA prior to the stereochemical revision. These include the developments of: (1) an anti-Felkin-selective C35–C36 oxygenated aldol reaction, (2) a Felkin-selective C18–C19 anti aldol reaction and its application to the synthesis of C9–C27 degradation fragment **9**, and (3) a Felkin-selective C15–C16 Mukaiyama aldol reaction.

A. The C35–C36 Oxygenated Aldol Reaction[25]

The C33–C37 lactol region of AsA presented us the opportunity to investigate diastereoselective construction of the C33–C36 anti/syn/anti tetraol by aldol reaction of an oxygenated enolate.[26] Concerns over controlling enolate geometry, enolization regioselectivity, and aldehyde facial selectivity were abated by the discovery of a highly selective C35–C36 oxygenated aldol reaction (Scheme 1.4). We observed exclusive formation of desired anti/syn/anti aldol adduct **23** by linking together the α- and β-oxygens of model aldehyde **20** with an acetonide protecting group. We propose that anti-Felkin addition of the more reactive (*E*) enolate[27] of ketone **21** to this aldehyde is favored and proceeds via Zimmerman-Traxler[28]

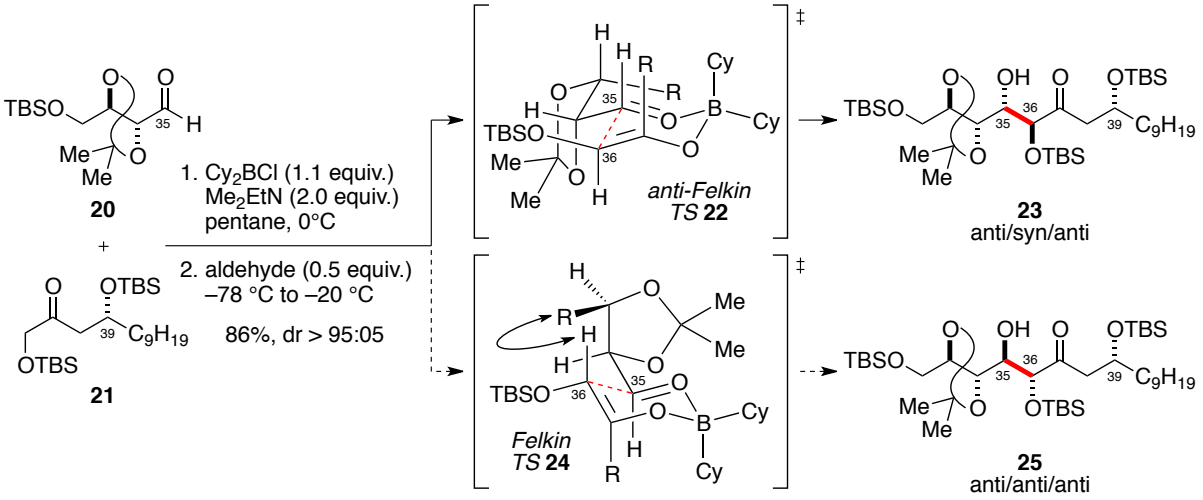
(25) This section represents the culminative work of Drs. Frank Glorius, Jing Zhang, and Jason D. Burch.

(26) (a) Glorius, F. *Development of α-Oxygenated Aldol Methodology and Progress Towards the Synthesis of Aflastatin A*. Postdoctoral Report, Harvard University, **2001**; (b) Evans, D.A.; Glorius, F.; Burch, J.D. *Org. Lett.* **2005**, *7*, 3331–3335.

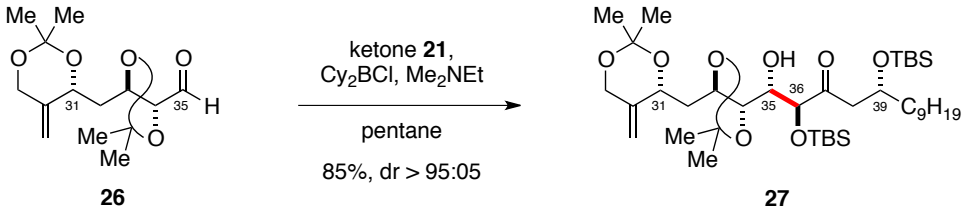
(27) Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.

transition state **22**. By contrast, we anticipate that the Felkin rotamer of aldehyde **20** destabilizes transition state **24** by introducing nonbonding interactions between the aldehyde side chain and the incoming enolate nucleophile.

Scheme 1.4. The C35–C36 oxygenated aldol reaction.



Ultimately, we determined that aldol diastereoselectivity was strongly dependent upon protecting group identity. As applied to the synthesis of AsA, installation of an acetonide protecting group at C33/C34 would be essential for anti-Felkin-selective C35–C36 bond formation. Upon satisfying this requirement, we successfully applied the oxygenated aldol reaction to the syntheses of AsA lactol region subunits **27** (eq 1)[29] and **29** (eq 2).[26b,30]

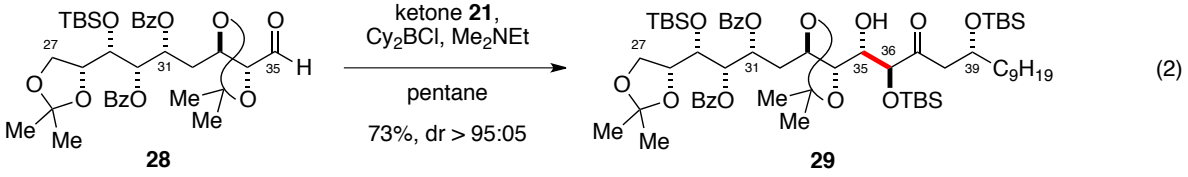


(1)

(28) Zimmerman, H.E.; Traxler, M.D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

(29) Zhang, J. *Studies Toward the Total Synthesis of (–)-Aflastatin A*. Postdoctoral Report, Harvard University, **2003**.

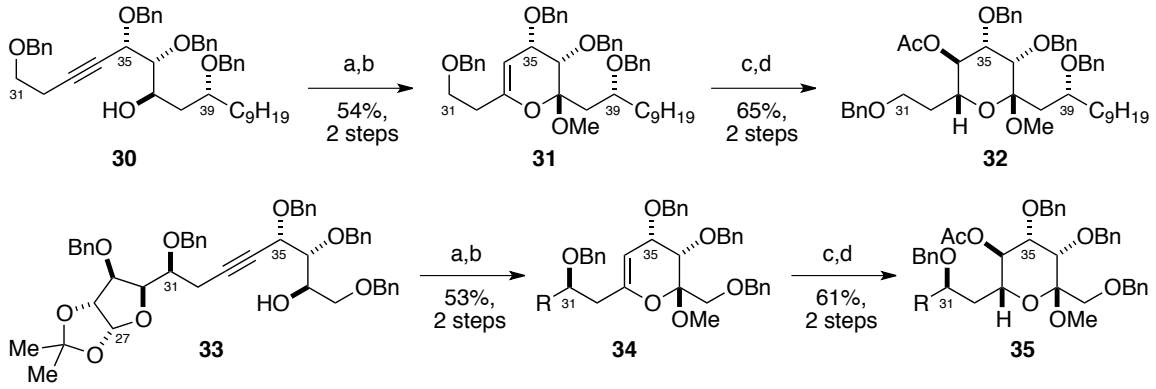
(30) Burch, J.D. *Complex Aldol Reactions for Polyketide Synthesis: I. Total Synthesis of Callipeltoside A. II. Synthesis of the C27–C48 Subunit of Aflastatin A*. Ph.D. Thesis, Harvard University, **2005**.



(2)

Recently, Ramana and coworkers reported an alternative approach to constructing the AsA lactol region.[31] Their syntheses featured the palladium-mediated 6-endo-dig cycloisomerization of alkynones directly obtained from the oxidation of alkynols **30** and **33** (Scheme 1.5). They then installed the requisite stereochemistry at C33 and C34 via face-selective hydroboration of intermediate dihydropyrans **31** and **34**. Their efforts ultimately led to the construction of lactol methyl ethers **32** and **35**, respectively.

Scheme 1.5. Ramana's syntheses of the AsA lactol region.



Reagents and conditions: (a) IBX, EtOAc, reflux; (b) $Pd(OAc)_2$, MeOH, rt, 54% (**31**, 2 steps), 53% (**34**, 2 steps); (c) BH_3•Me_2S, THF, 0 °C; H_2O_2, NaOH (aq.), rt; (d) Ac_2O, py, CH_2Cl_2, rt, 65% (**32**, 2 steps), 61% (**35**, 2 steps).

B. The C18–C19 Aldol Reaction and Synthesis of the C9–C27 Degradation Fragment[32]

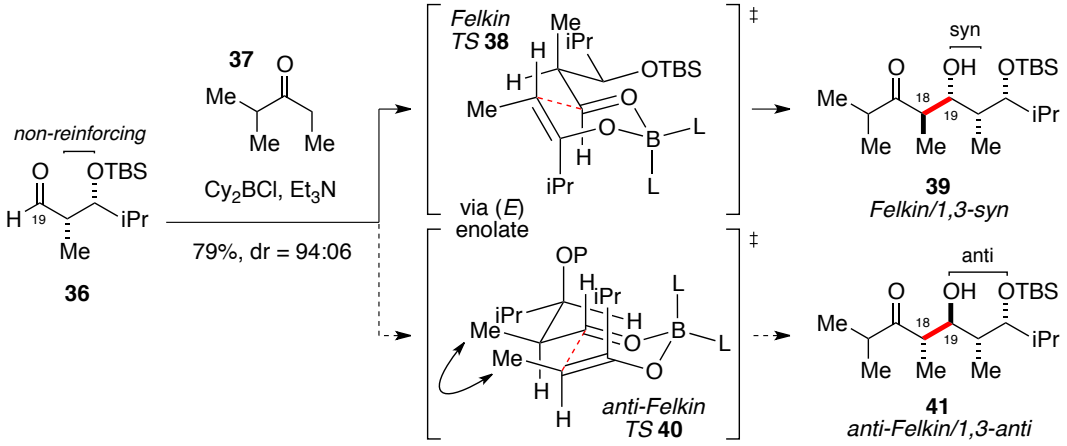
Soon after Kishi and coworkers questioned the initial stereochemical assignment of AsA,[21b] the Evans group prioritized confirmation of the relative and absolute stereochemistry of C9–C27 degradation fragment **9** by chemical synthesis. Our strategy was based on the

(31) (a) Narute, S.B.; Kiran, N.C.; Ramana, C.V. *Org. Biomol. Chem.* **2011**, *9*, 5469–5475; (b) Narute, S.B.; Ramana, C.V. *Tetrahedron* **2013**, *69*, 1830–1840.

(32) This section represents the culminative work of Drs. William C. Trenkle and Jing Zhang.

Felkin-selective anti aldol addition of ethyl ketone **37** to α,β-syn-aldehyde **36** (Scheme 1.6).[33] Despite the non-reinforcing relationship between vicinal substituents on the aldehyde,[34] Felkin adduct **39** is still formed with high diastereoselection due to the inherent Felkin bias of the preformed (*E*) enolate.[33b] As seen in transition state **40**, formation of undesired anti-Felkin product **41** is disfavored due to a syn pentane interaction that develops during C–C bond formation.

Scheme 1.6. Precedent for the C18–C19 anti aldol reaction.



Our group then successfully applied this anti aldol reaction to the synthesis of AsA C9–C27 degradation fragment **9**.[29,35] Addition of the (*E*) enolate of ethyl ketone **42** to aldehyde **43** provided the desired anti adduct **44** and its C18 epimer in moderate yield and excellent Felkin diastereoselectivity (Scheme 1.7). The undesired diastereomer arose from unfortunate epimerization of the major product under the reaction conditions. We then converted aldol adduct **44** to degradation fragment **9** and its derivative peracetate, compared their analytical data with authentic samples,[15,16] and concluded that Sakuda and coworkers had

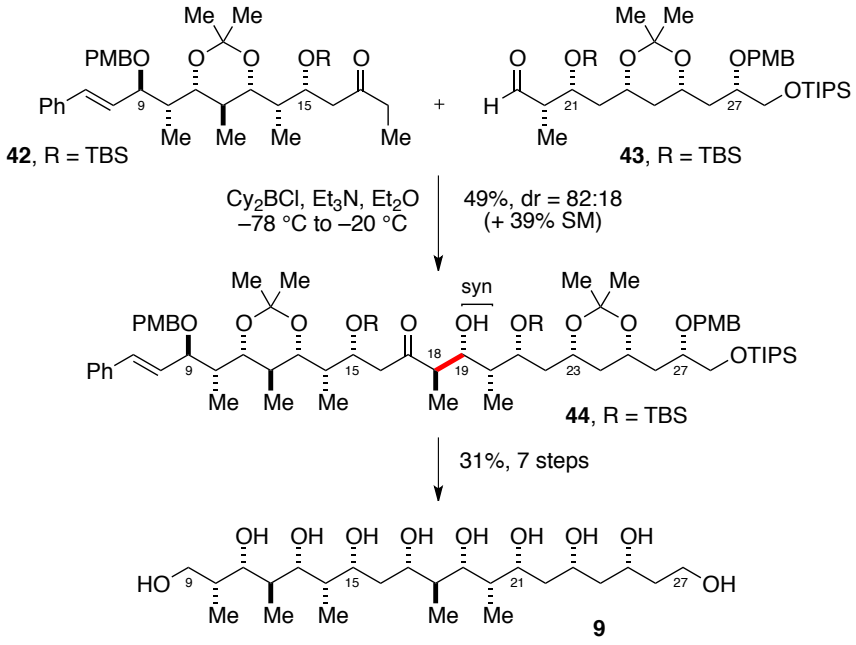
(33) (a) Dart, M.J. *Diastereoselective Aldol Addition Reactions*. Ph.D. Thesis, Harvard University, **1995**; (b) Evans, D.A.; Dart, M.J.; Duffy, J.L.; Rieger, D.L. *J. Am. Chem. Soc.* **1995**, *117*, 9073–9074.

(34) Evans, D.A.; Dart, M.J.; Duffy, J.L.; Yang, M.G. *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.

(35) Evans, D.A.; Trenkle, W.C.; Zhang, J.; Burch, J.D. *Org. Lett.* **2005**, *7*, 3335–3338.

correctly assigned the relative and absolute stereochemistry of the AsA C9–C27 degradation fragment **9**.

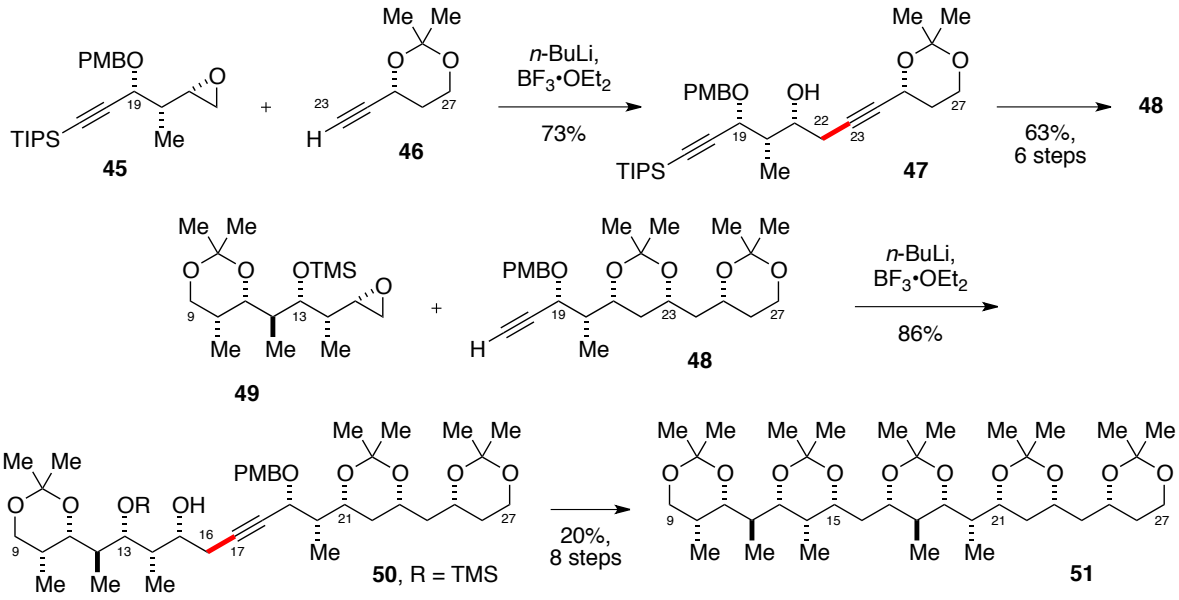
Scheme 1.7. Synthesis of AsA C9–C27 degradation fragment **9**.



More recently, Robles and McDonald reported an alternative approach to constructing the pentaacetonide derivative of AsA degradation fragment **9**.[36] Their strategy for the synthesis of the C9–C27 polyketide region relied on iterative additions of lithium acetylides to epoxides, followed by regio- and stereoselective functionalization of the resultant internal alkynes (Scheme 1.8). Their efforts resulted in the modular synthesis of pentaacetonide **51**, which matched original spectral data provided by the isolation group.

(36) (a) Robles, O.; McDonald, F.E. *Org. Lett.* **2008**, *10*, 1811–1814; (b) Robles-Resendiz, O. *Modular Synthesis of Polyketide Natural Products: Synthesis of the C9–C27 Degradation Product of Aflastatin A and Total Synthesis of Fostriecin*. Ph.D. Thesis, Emory University, **2009**.

Scheme 1.8. McDonald's synthesis of AsA C9–C27 degradation fragment **51**.



C. The C15–C16 Mukaiyama Aldol Reaction[37]

The C18–C19 aldol reaction was key to providing us access to degradation fragment **9** and verification of its structural assignment. Nevertheless, we desired a more convergent fragment coupling for the synthesis of AsA, and found recourse in a Felkin-selective C15–C16 Mukaiyama aldol reaction. Our approach was based on the trityl-catalyzed[38] addition of enolsilane **53** to syn aldehyde **52** to selectively form Felkin aldol adduct **54** despite non-reinforcing α,β-stereoinduction (Scheme 1.9).[34] We propose that sterically demanding Lewis acids such as the trityl cation increase the influence of the α-methyl stereocenter by promoting addition through antiperiplanar transition state **56**,[39] perhaps with an altered nucleophile trajectory.[40]

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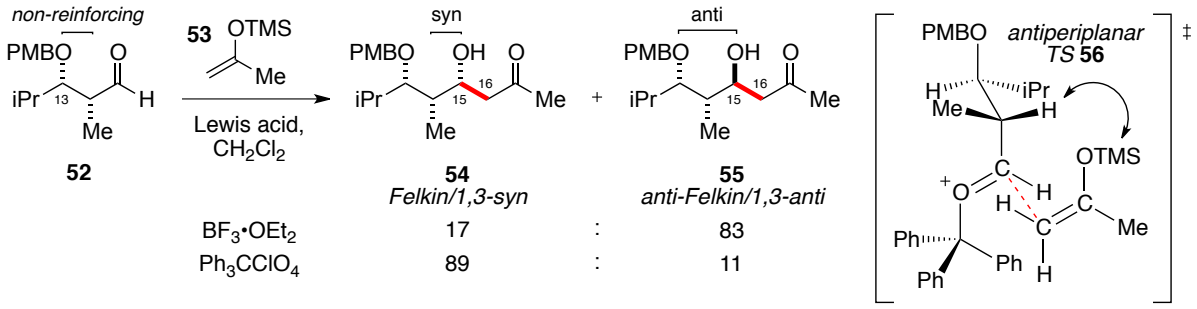
(37) This section represents the culminative work of Drs. William C. Trenkle, Jing Zhang, and Joseph M. Young.

(38) (a) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, *13*, 1759–1762; (b) Denmark, S.E.; Chen, C.-T. *Tetrahedron Lett.* **1994**, *35*, 4327–4330.

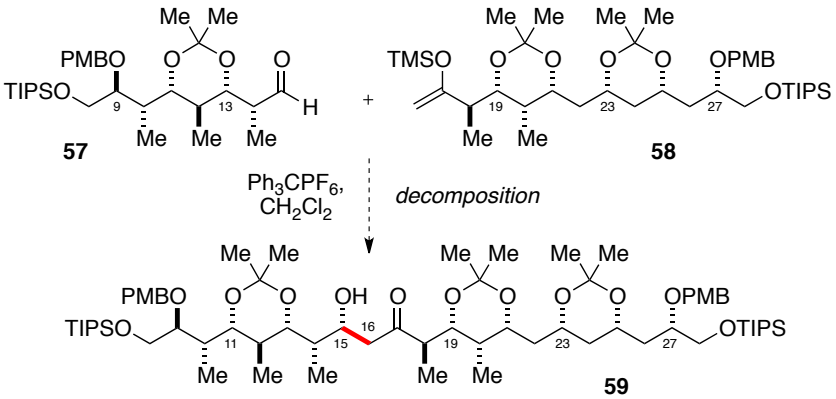
(39) Heathcock, C.H.; Walker, M.A. *J. Org. Chem.* **1991**, *56*, 5747–5750 and references therein.

(40) Heathcock, C.H.; Flippin, L.A. *J. Am. Chem. Soc.* **1983**, *105*, 1667–1668.

Scheme 1.9. Precedent for the C15–C16 Mukaiyama aldol reaction.

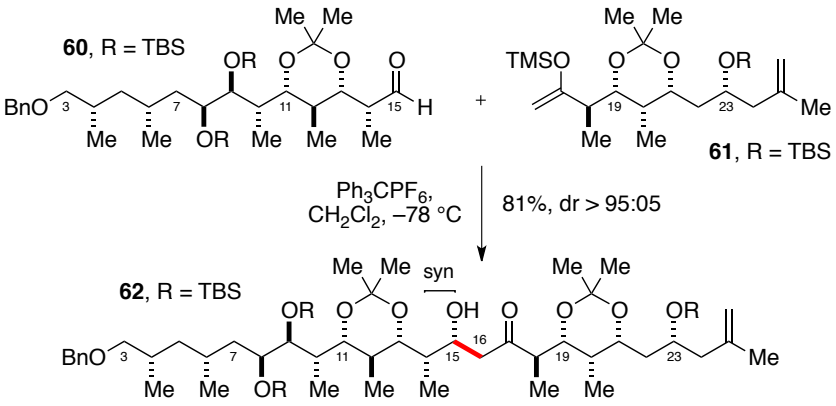


Our initial attempts at the trityl-catalyzed C15–C16 Mukaiyama aldol addition of enolsilane **58** to aldehyde **57** were met with decomposition (eq 3).[41] We later identified that the likely origin of decomposition was the C27 PMB ether of enolsilane **58**.[24] Since the trityl cation is known to oxidize unhindered PMB ethers via hydride abstraction,[42] new aldol coupling partners were designed to exclude this protecting group. Ultimately, addition of enolsilane **61** to aldehyde **60** provided the desired Felkin aldol adduct **62** as a single C15 diastereomer (eq 4). This result demonstrated that construction of the AsA C3–C26 polyketide region could be achieved with greater convergence and efficiency.



(41) Trenkle, W.C. *Progress Towards the Synthesis of Aflastatin A*. Postdoctoral Report, Harvard University, **2002**.

(42) For examples, see: (a) Fujioka, H.; Sawama, Y.; Kotoku, N.; Ohnaka, T.; Okitsu, T.; Murata, N.; Kubo, O.; Li, R.; Kita, Y. *Chem. Eur. J.* **2007**, *13*, 10225–10238; (b) Yadav, V.K.; Agrawal, D. *Chem. Commun.* **2007**, 5232–5234; (c) Doddi, V.R.; Kokatla, H.P.; Pal, A.P.J.; Basak, R.K.; Vankar, Y.D. *Eur. J. Org. Chem.* **2008**, 5731–5739.



(4)

Shortly after our discovery of a competent C15–C16 Mukaiyama aldol reaction, Sakuda and coworkers revised the initial stereochemical assignment of AsA.[23] In response, we prioritized the synthesis of C3–C48 degradation fragment **19** as a means of confirming the relative and absolute stereochemistry of AsA. Although the structural reassignment required us to revisit our synthesis plans, we were confident in the structural identity of the C9–C27 region, and could use both the C35–C36 oxygenated aldol and C15–C16 Mukaiyama aldol reactions in our future synthesis efforts. Our synthesis of AsA C3–C48 degradation fragment **19** will be discussed in Chapter 2.

Chapter

2

Synthesis of the C3–C48 Degradation Fragment of Aflastatin A

I. Synthesis Plans Involving C28–C29 Bond Formation

The structure of aflastatin A (AsA) presented our group the opportunity to develop aldol chemistry for the construction of its densely oxygenated C27–C31 and C33–C37 regions. In addition to developing an anti-Felkin-selective C35–C36 oxygenated aldol reaction, our group targeted the C27–C31 pentaol as a site for major fragment coupling. Initially, our retrosynthesis plan hinged on the development of a C28–C29 oxygenated aldol reaction, but was later transformed by the discovery of a C26–C27 chelate-controlled aldol addition.

A. Initial Structure of Aflastatin A[1]

Our first retrosynthesis plan for the initial structure of AsA (**1**) involved disconnection at C2–C3 to produce tetramic acid derivative **2** (Scheme 2.1).[2] We planned to install the tetramic acid by a Horner-Wadsworth-Emmons reaction[3] as late in the synthesis as possible

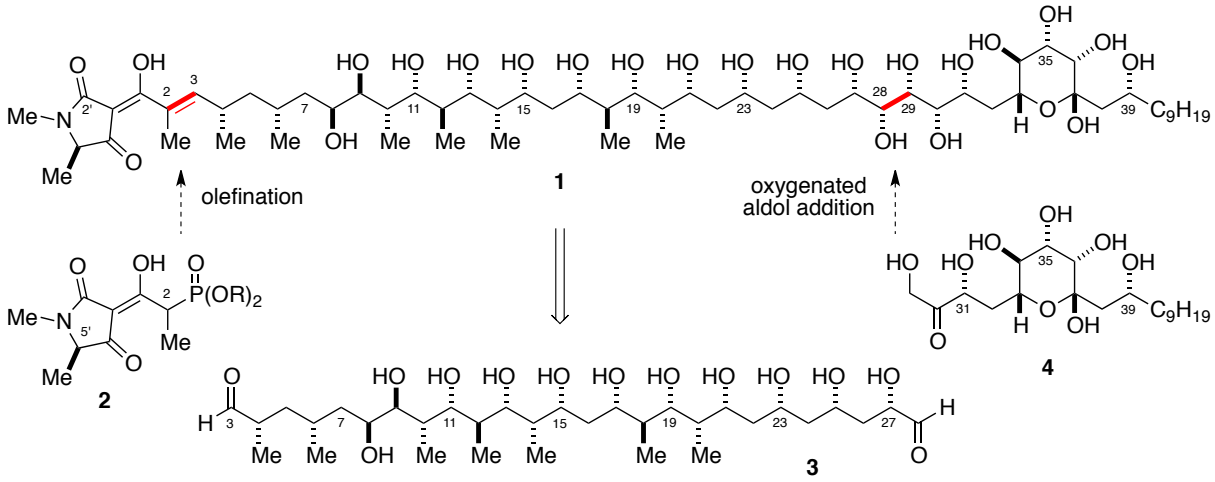
(1) This section represents the culminative work of Dr. William C. Trenkle and Dr. Jing Zhang.

(2) Trenkle, W.C. *Progress Towards the Synthesis of Aflastatin A*. Postdoctoral Report, Harvard University, **2002**.

(3) (a) Horner, L.; Hoffman, H.; Wippel, H.G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499–2505; (b) Wadsworth, W.S., Jr.; Emmons, W.D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.

because we expected that the C5' stereocenter would be readily epimerizable.[4] Having removed this base-sensitive moiety, we next focused on an aldol-based assemblage of the C3–C48 polyketide backbone. For the major fragment coupling, we decided to investigate the double-stereodifferentiating syn aldol addition of ketone **4** to dialdehyde synthon **3** as a means of forming the C28–C29 bond.

Scheme 2.1. First retrosynthesis plan for structure **1**.



At the time, double-stereodifferentiating syn aldol additions of α'-oxygenated ketones to α-oxygenated aldehydes were undocumented. Although syn aldol reactions of chiral α'-oxygenated ketones with achiral aldehydes were known to favor the formation of 1,3-syn products,[5] the effect of introducing a second stereocontrol element at the aldehyde's α-position was not well understood. As per the polar Felkin-Anh model,[6] we predicted that the aldehyde α-alkoxy stereocenter at C27 would establish a matched relationship with the C31

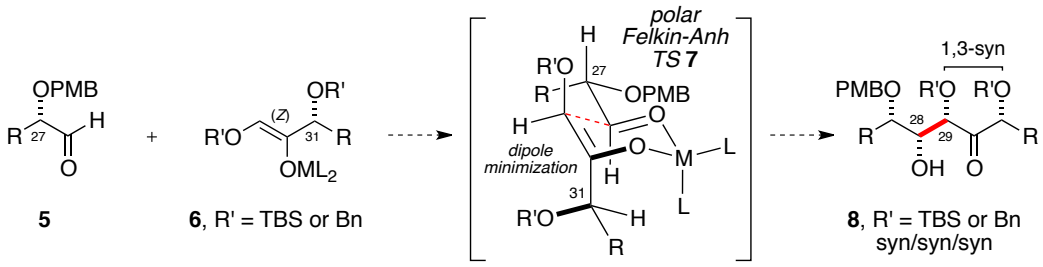
(4) Royles, B.J.L. *Chem. Rev.* **1995**, *95*, 1981–2001 and references therein.

(5) (a) Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566–1568; (b) Marco, J.A.; Carda, M.; Falomir, E.; Palomo, C.; Oiarbide, M.; Ortiz, J.A.; Linden, A. *Tetrahedron Lett.* **1999**, *40*, 1065–1068; (c) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J.A. *Tetrahedron* **2000**, *56*, 677–683.

(6) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199–2204; (b) Anh, N.T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70; (c) Anh, N.T. *Top. Curr. Chem.* **1980**, *88*, 145–162.

stereocenter of (*Z*) enolate **6**. Aldol reaction via transition state **7** would effect diastereoselective C28–C29 bond formation, and thereby lead to the desired syn/syn/syn adduct **8** (Scheme 2.2). We envisioned that transition state **7** would be favored since it features hyperconjugative stabilization of the forming C28–C29 bond, dipole-dipole minimization between the C31 α'-alkoxy stereocenter and the transforming enolate, and minimization of nonbonding interactions between the reacting partners.

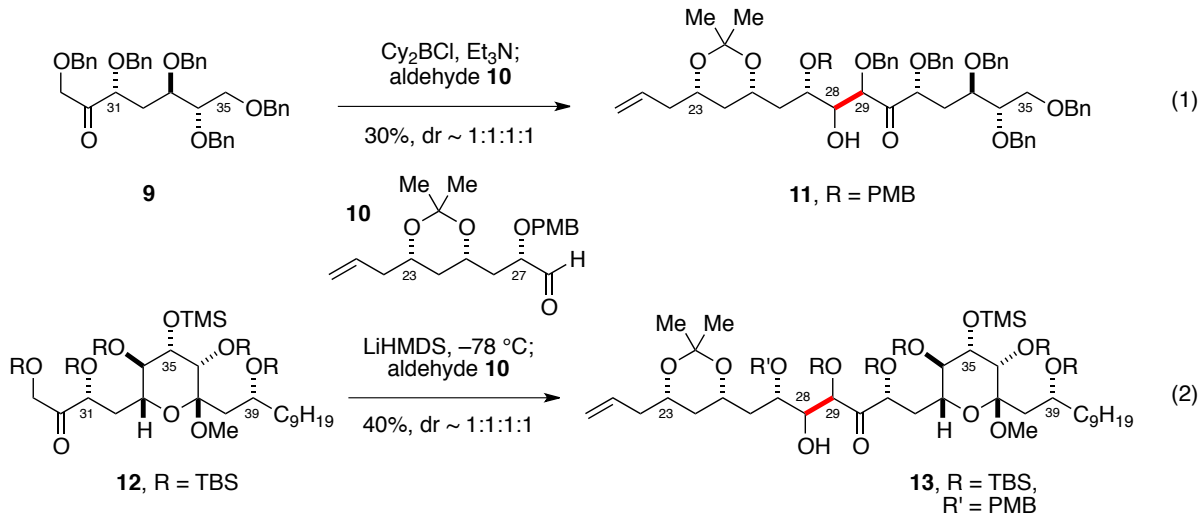
Scheme 2.2. Proposed C28–C29 oxygenated aldol reaction.



Model studies of the C28–C29 oxygenated aldol reaction were then performed to evaluate our stereochemical prediction.[7] Our desires to control enolization regioselectivity and produce geometrically-defined (*Z*) enolates of general structure **6** were satisfied by reports of chlorodicyclohexylborane-mediated syn aldol additions of ketones bearing both chelating alkyl and bulky silyl protecting groups at their α'-oxygen position (C31).[8] Disappointingly, reaction of ketone **9** with aldehyde **10** under these conditions proceeded poorly in both yield and diastereoselectivity (eq 1). Boron-mediated enolization of advanced C29–C48 ketone **12** was also attempted, but reactivity – and similarly poor levels of diastereoselection – was observed only upon formation of the corresponding lithium enolates (eq 2).

(7) Zhang, J. *Studies Toward the Total Synthesis of (–)-Aflastatin A*. Postdoctoral Report, Harvard University, **2003**.

(8) Murga, J.; Falomir, E.; Carda, M.; González, Marco, J.A. *Org. Lett.* **2001**, *3*, 901–904.

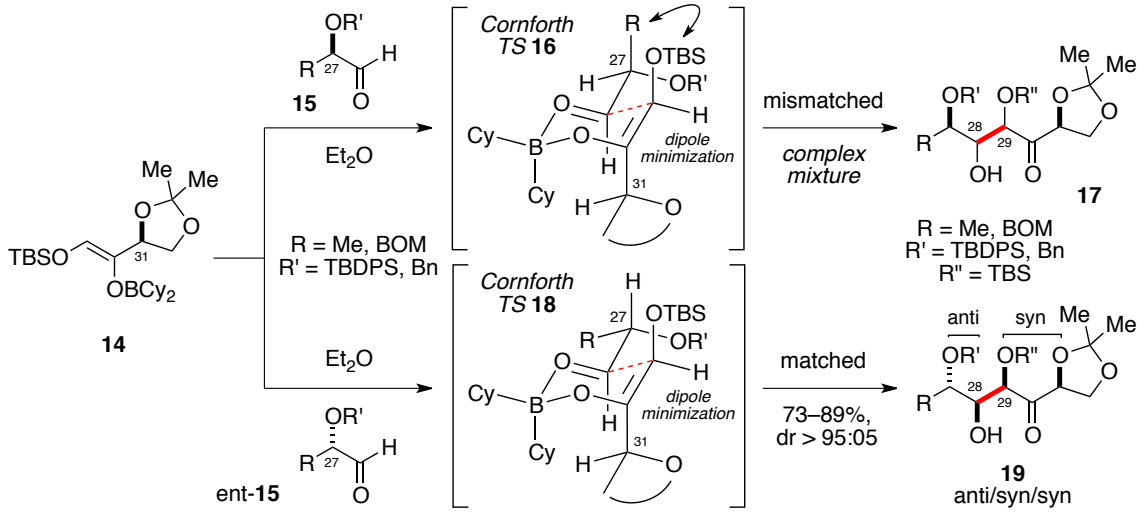


During the course of these studies, related work in the Evans group demonstrated that the modified Cornforth model provides a more accurate description of enolate additions to α-alkoxy aldehydes than the polar Felkin-Anh model.[9] Shortly thereafter, Marco, Carda and coworkers reported double-stereodifferentiating boron aldol reactions of an erythulose-derived α,α'-dioxygenated ketone with both enantiomeric series of α-oxygenated aldehydes **15** (Scheme 2.3).[10] Addition of (*Z*) boron enolate **14** to aldehydes **15** having the same relative stereochemistry required for the C28–C29 aldol reaction produced a complex mixture of aldol adducts **17**, thus agreeing with our model studies. Reaction of the same chiral enolate with enantiomeric aldehyde ent-**15** established a matched stereorelationship between these reacting partners and resulted in the formation of anti/syn/syn aldol adducts **19** in high yield and excellent diastereoselectivity.

(9) (a) Evans, D.A.; Siska, S.J.; Cee, V.J. *Angew. Chem., Int Ed.* **2003**, *42*, 1761–1765; (b) Siska, S.J. *Construction of Polyhydroxylated Stereoarrays Using the Aldol Reaction*. Ph.D. Thesis, Harvard University, **2005**.

(10) (a) Marco, J.A.; Carda, M.; Díaz-Oltra, S.; Murga, J.; Falomir, E.; Roeper, H. *J. Org. Chem.* **2003**, *68*, 8577–8582; (b) Díaz-Oltra, S.; Murga, J.; Falomir, E.; Carda, M.; Peris, G.; Marco, J.A. *J. Org. Chem.* **2005**, *70*, 8130–8139.

Scheme 2.3. Double stereodifferentiating aldol reactions that support the Cornforth model.



B. Revised Structure of Aflastatin A[11]

Overall, these experiments provided support for the modified Cornforth model in aldol additions of substituted enolates to α-oxygenated aldehydes. As a result, we deemed that proposed transition state **7** (Scheme 2.2) was likely invalid, and realized that relying upon a C28–C29 oxygenated aldol reaction for construction of the initially proposed structure of AsA (**1**) was untenable. Fortunately, the stereochemical revision of the C27–C31 pentaol region of AsA[12] provided us an opportunity to revisit this disconnection as an alternative to the C26–C27 aldol chemistry that will be described in due course. One of our retrosynthesis plans for AsA C3–C48 degradation fragment **20**[13] involved disconnection at C28–C29 to produce aldehyde **21** and the C31-epimer **22** of the original ketone fragment (Scheme 2.4).[14]

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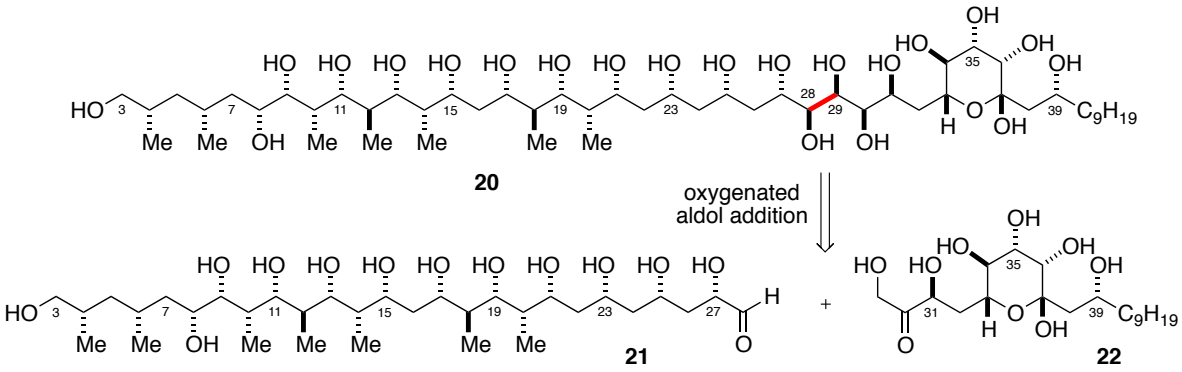
(11) The synthesis of C27–C31 pentaol derivative **25** (*vide infra*) was performed by the author in collaboration with Dr. Joseph M. Young and Dr. Egmont Kattnig.

(12) (a) Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379–14393; (b) Sakuda, S.; Matsumori, N.; Furihata, K.; Nagasawa, H. *Tetrahedron Lett.* **2007**, *48*, 2527–2531; (c) Sakuda, S.; Yoshinari, T.; Nakamura, K.; Akiyama, T.; Takahashi, Y.; Muraoka, Y.; Nonomura, Y.; Nagasawa, H. *Mycotoxins* **2006**, *Suppl. 4*, 135–140.

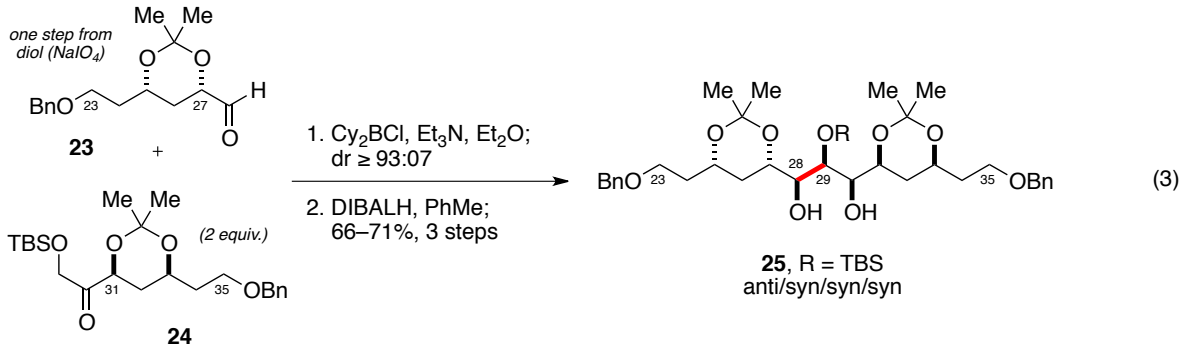
(13) Ikeda, H.; Matsumori, N.; Ono, M.; Suzuki, A.; Isogai, A.; Nagasawa, H.; Sakuda, S. *J. Org. Chem.* **2000**, *65*, 438–444.

(14) Young, J.M. *Studies Toward the Synthesis of Aflastatin A*. Ph.D. Thesis, Harvard University, **2008**.

Scheme 2.4. C28–C29 aldol-based retrosynthesis plan for C3–C48 degradation fragment **20**.



Synthesis of the AsA C27–C31 anti/syn/syn/syn pentaol region by this double-stereodifferentiating aldol strategy required selection of protecting groups that did not interfere with reactivity or diastereoselectivity. Previous experiments revealed that sterically encumbered ketones (such as **12**, eq 2) resist enolization by chlorodicyclohexylborane,[7] and that bulky aldehydes display limited reactivity with simple boron enolates.[15] We alleviated these concerns by tying back both the C27 and C31 stereocenters as their respective 1,3-syn acetonides. Gratifyingly, the model reaction of the dicyclohexylboron enolate of α-silyloxy ketone **24** with aldehyde **23** produced the desired aldol adduct with high levels of conversion and diastereoselection (eq 3). The intermediate β-hydroxy ketone was subsequently reduced with diisobutylalane[16] to afford the desired pentaol derivative **25** in good overall yield.



(15) Burch, J.D. *Complex Aldol Reactions for Polyketide Synthesis: I. Total Synthesis of Callipeltoside A. II. Synthesis of the C27–C48 Subunit of Aflastatin A*. Ph.D. Thesis, Harvard University, **2005**.

(16) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett*. **1986**, *27*, 3009–3012.

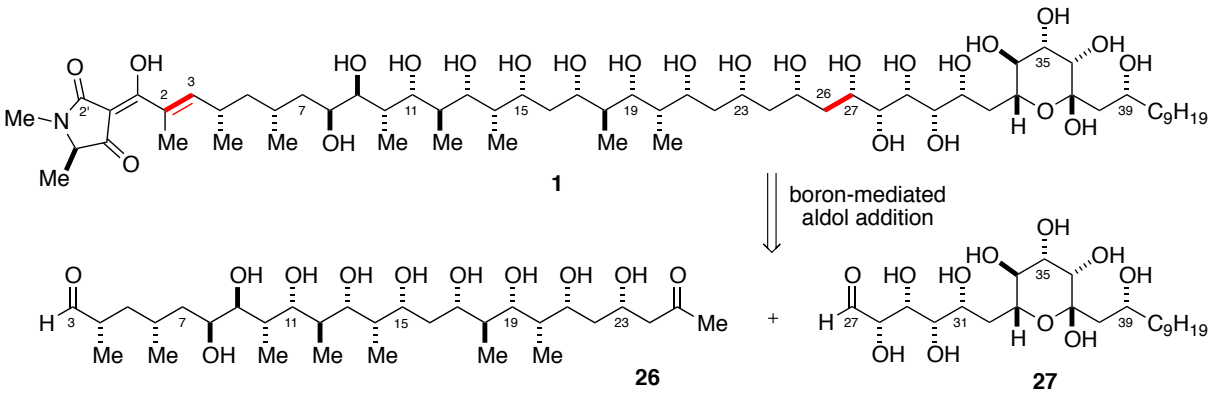
This result demonstrated the potential of oxygenated enolate chemistry in constructing the C27–C31 pentaol region of AsA. As a major fragment coupling, however, we noted that the C28–C29 aldol addition was limited by both the relative stoichiometry and protecting group requirements of its reacting partners. We therefore refocused our efforts on the development and implementation of a C26–C27 chelate-controlled aldol addition.

II. Synthesis Plans Involving C26–C27 Bond Formation

A. Initial Structure of Aflastatin A[17]

As experimental support for the modified Cornforth model grew, our group began to explore other possibilities for major fragment coupling within the C27–C31 pentaol region. Our second retrosynthesis plan for the initial structure of AsA (**1**) abandoned the idea of a C28–C29 oxygenated aldol reaction and instead focused on forming the C26–C27 bond by boron-mediated aldol addition of methyl ketone **26** to poly-hydroxylated aldehyde synthon **27** (Scheme 2.5).[15]

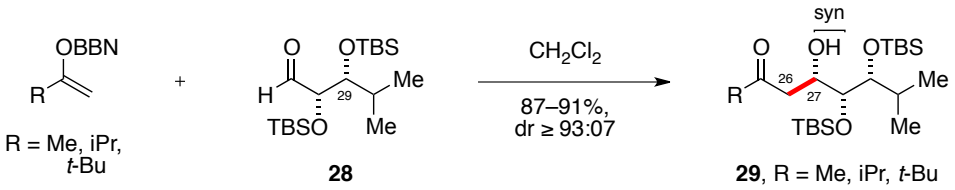
Scheme 2.5. Second retrosynthesis plan for structure **1**.



The newly proposed disconnection at C26–C27 was borne out of our group's systematic study of methyl ketone aldol additions to α,β-bisoxygenated aldehydes under

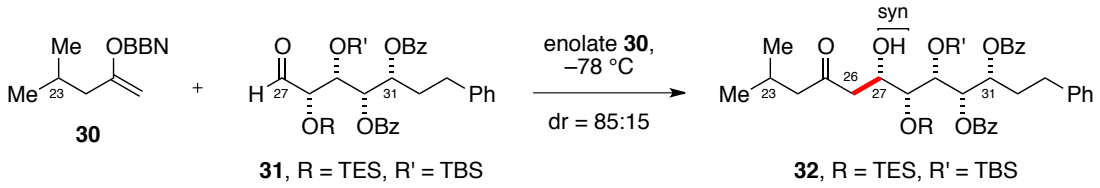
(17) This section represents the culminative work of Drs. Victor J. Cee, Sarah J. Siska, and Jason D. Burch.

nonchelating conditions.[18] We observed synthetically useful levels of diastereoselectivity for the desired 1,2-syn aldol adducts **30** when enolboranes were added to syn aldehyde **28**, in which both α- and β-oxygen substituents were protected as TBS ethers (eq 4).



(4)

This reaction was then extended to model substrates that possessed the full oxygenation pattern present in the C28–C31 region of AsA. Aldol addition of 9-BBN enolate **30** derived from isobutyl methyl ketone to aldehyde **31** afforded the desired 1,2-syn adduct with slightly diminished diastereoselection (eq 5).[15] Notably, the size of the protecting groups on C30 and C31 was minimized (benzoates were selected instead of TBS ethers) to ensure reactivity.

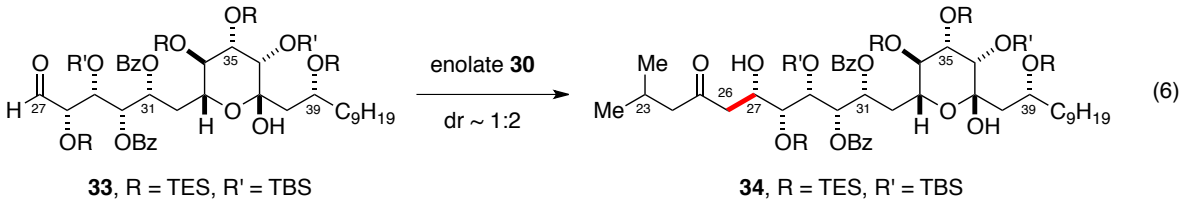


(5)

To our surprise, reaction of the same enolborane with fully elaborated C27–C48 aldehyde **33** proceeded with inverted diastereoselectivity (eq 6), even though the first point of difference between aldehydes **31** and **33** occurred at C33.[15] This experiment showed that formation of the C33–C37 lactol prior to major fragment coupling could have an adverse effect on reaction diastereoselectivity. As a result, future synthesis plans centered upon C26–C27 bond formation as the major fragment coupling would involve additions to the open-

(18) Evans, D.A.; Cee, V.J.; Siska, S.J. *J. Am. Chem. Soc.* **2006**, *126*, 9433–9441.

chain form of the C27–C48 lactol region. Lactol formation would then be delayed until a later stage in the synthesis, such as global deprotection.



33, R = TES, R' = TBS

34, R = TES, R' = TBS

(6)

B. Revised Structure of Aflastatin A[19]

As before, the stereochemical revision of the C27–C31 pentaol region of AsA provided us an opportunity to modify our major fragment coupling strategy. However, before completing the total synthesis of AsA, we sought to confirm its stereochemical reassignment[12] by way of C3–C48 degradation fragment **20**.[13] We envisioned polyol **20** to arise from the diastereoselective aldol addition of C3–C26 ketone **35** to C27–C48 aldehyde **36** (Scheme 2.6).[14,20] Aldehyde **36**, possessing both α- and β-oxygenation, offered us the possibility of using chelation control[21] to establish the stereocenter at C27 with high diastereoselection. We expected that nucleophilic addition to a six-membered chelate would afford the desired 1,3-anti relationship. Since silyl ethers generally disfavor chelation,[22,23] we planned to induce chelation between the carbonyl and β-benzyloxy substituent (at C29) by protecting the C28 carbinol as its silyl ether.

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(19) This section represents the culminative work of Drs. Victor J. Cee, and Egmont Kattnig. Dr. Kattnig is credited with the discovery and development of the chelate-controlled/soft enolization-based C26–C27 aldol reaction (*vide infra*).

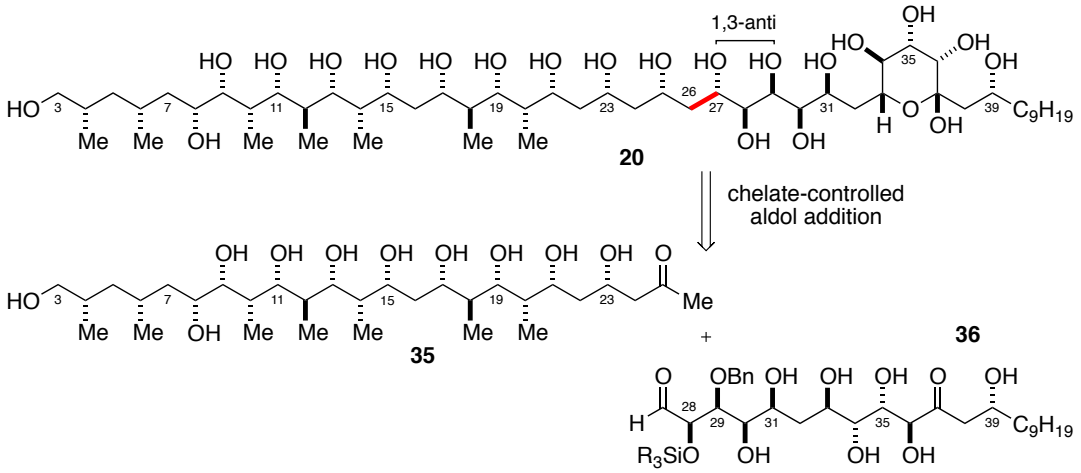
(20) Kattnig, E. *An Aldol Approach Toward Aflastatin A – Synthesis of the C3–C48 Polyol*. Postdoctoral Report, Harvard University, **2011**.

(21) (a) Reetz, M.T. *Angew. Chem.* **1984**, *96*, 542–555; *Angew. Chem., Int. Ed.* **1984**, *23*, 556–569; (b) Reetz, M.T. *Acc. Chem. Res.* **1993**, *26*, 462–468 and references therein.

(22) Keck, G.E.; Boden, E.P. *Tetrahedron Lett.* **1984**, *25*, 265–268.

(23) For exceptions, see: a) Evans, D.A.; Allison, B.D.; Yang, M.G.; Masse, C.E. *J. Am. Chem. Soc.* **2001**, *123*, 10840–10852; b) Stanton, G.R.; Kauffman, M.C.; Walsh, P.J. *Org. Lett.* **2012**, *14*, 3368–3371 and references therein.

Scheme 2.6. C26–C27 aldol-based retrosynthesis plan for C3–C48 degradation fragment **20**.



In developing this strategy, we were encouraged by our earlier systematic study[24] of methyl ketone Mukaiyama aldol additions[25] to α,β-bisoxygenated aldehydes under chelating conditions.[26] For these experiments, magnesium(II) iodide was chosen as the Lewis acid because it was known to chelate heteroatom-substituted aldehydes and promote highly diastereoselective Mukaiyama aldol reactions.[27] Gratifyingly, enolsilane additions to syn α-silyloxy, β-alkoxy aldehyde **37** in the presence of freshly prepared MgI_2 proceeded in high yield to afford the desired 1,3-anti products **39** as single diastereomers (Scheme 2.7).[28] The observed selectivity is consistent with 1,3-chelate model **38**, whereby nucleophilic addition to the carbonyl occurs preferentially from the less sterically hindered face of the six-membered chelate. In this model, the two stereocenters of the syn diastereomer are reinforcing, as aldol

(24) Cee, V.J. *I. Asymmetric Induction in Heteroatom-Substituted Aldehydes. II. Total Synthesis of (+)-Casuarine*. Ph.D. Thesis, Harvard University, **2003**.

(25) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett* **1973**, 1011–1014; (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc*. **1974**, *96*, 7503–7509; (c) Mukaiyama, T. *Angew. Chem*. **2004**, *116*, 5708–5733; *Angew. Chem., Int. Ed*. **2000**, *43*, 5590–5614.

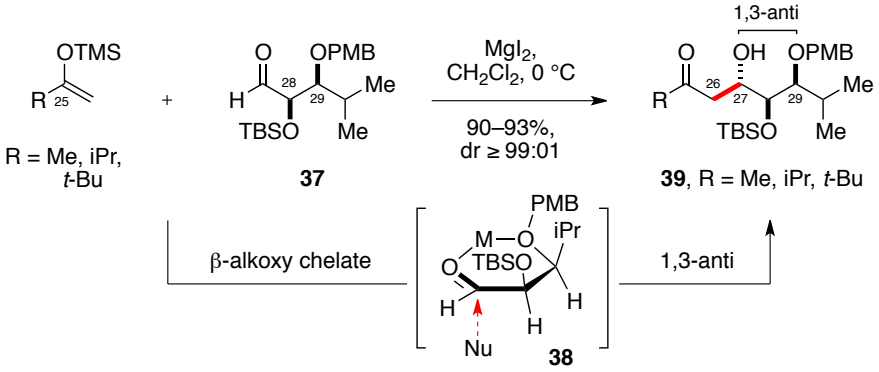
(26) For the analogous study under nonchelating conditions, see: Ref. 18.

(27) For an example, see: Corey, E.J.; Li, W.; Reichard, G.A. *J. Am. Chem. Soc*. **1998**, *120*, 2330–2336.

(28) The stereochemistry of the newly formed stereogenic center was determined by Mosher ester analysis. See: (a) Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc*. **1973**, *95*, 512–519; (b) Hoye, T.R.; Jeffrey, C.S.; Shao, F. *Nat. Protoc*. **2007**, *2*, 2451–2458.

addition to the *Re* face of aldehyde **37** is blocked by both the α-silyloxy and β-alkyl substituents.[23a] Having realized the feasibility of using a chelate-controlled Mukaiyama aldol addition to form the C26–C27 bond, we opted to investigate the coupling of more complex substrates.

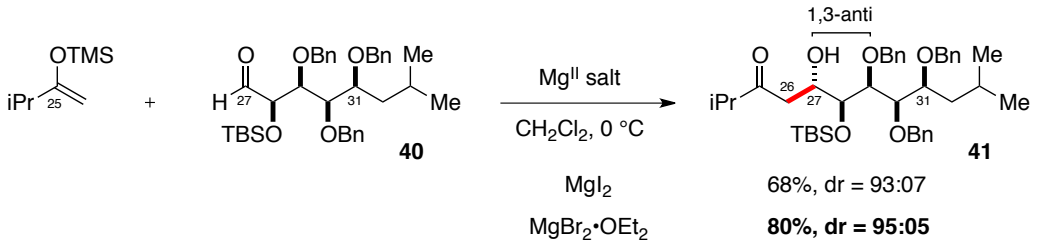
Scheme 2.7. Precedent for C26–C27 chelate-controlled aldol addition.



Our model studies began with the further elaboration of aldehyde fragment **37** (eq 7). The influence of additional oxygen-based stereocenters (and therefore protecting groups) at C30 and C31 on the diastereoselectivity of the fragment coupling was unknown. Aldehyde **40** was chosen as a suitable model since it featured the first four stereocenters (C28–C31) present in subunit **36**, while maintaining the requisite α-silyloxy and β-alkoxy substituents at C28 and C29, respectively. In an effort to minimize any potential steric effects on aldehyde reactivity, we also protected the neighboring stereocenters (C30 and C31) as benzyl ethers. Addition of the enolsilane derived from 3-methyl-2-butanone to aldehyde **40** in the presence of MgI_2 again produced the desired aldol adduct **41** in good yield and excellent diastereoselectivity, but we noted that freshly prepared $MgBr_2$•OEt_2 was more efficient at promoting this reaction.[29] In either experiment, the remote benzyloxy substituents at C30 and C31 did not

(29) For another example in which $MgBr_2$•OEt_2 was found to be superior to MgI_2, see: Evans, D.A.; Kvœrnø, L.; Dunn, T.B.; Beauchemin, A.; Raymer, B.; Mulder, J.A.; Olhava, E.J.; Juhl, M.; Kagechika, K.; Favor, D.A. *J. Am. Chem. Soc.* **2008**, *130*, 16295–16309.

significantly diminish the 1,3-anti diastereoselectivity of the aldol addition, and ultimately provided us a viable protecting group strategy for the C28–C31 stereotetrad during the key fragment coupling.



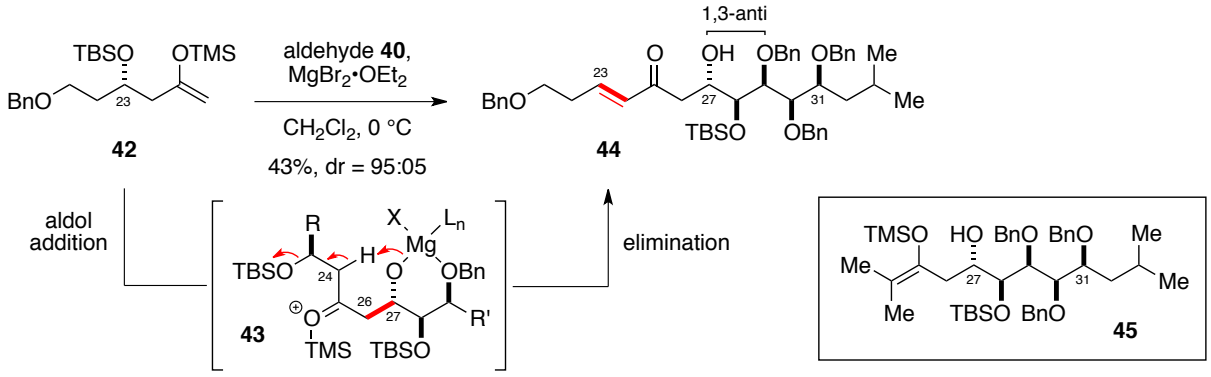
(7)

Our model studies continued with an investigation into the reactivity of model enolsilane **42** which incorporates the C23 carbinol of ketone fragment **35** protected as its silyl ether (Scheme 2.8). Magnesium-promoted aldol addition of enolsilane **42** to aldehyde **40** proceeded with excellent 1,3-anti diastereoselectivity, but unexpectedly resulted in elimination of the C23 silyloxy substituent to produce enone **44**. Formation of this undesired elimination product might be explained by the intermediacy of oxocarbenium ion **43**.[25] When silylation of the nascent C27 oxyanion is slowed by steric hindrance,[30] we propose that this alkoxide may instead abstract a proton from C24, ultimately resulting in departure of the vicinal silyloxy group. Further inspection of our previous reactions (eq 7) revealed the formation of enolsilane **45** prior to workup, presumably via an analogous deprotonation pathway.[31] When various attempts to prevent elimination by facilitating silyl transfer or quenching magnesium aldolate **43** *in situ* were unsuccessful, we found recourse in soft enolization.

(30) Intermolecular silyl transfer may be operative. For examples, see: Carreira, E.M.; Singer, R.A.; *Tetrahedron Lett*. **1994**, *35*, 4323; Denmark, S.E.; Chen, C.-T. *Tetrahedron Lett*. **1994**, *35*, 4327.

(31) Our group noted the formation of similar byproducts during the synthesis of azaspiracid. See: Dunn, T.B. *Synthesis of the C21–C40 Fragment of Azaspiracid-1*. Ph.D. Thesis, Harvard University, **2005**.

Scheme 2.8. Model C26–C27 Mukaiyama aldol reaction.



Soft enolization[32] is a powerful method for generating metal enolates under mild conditions. Our lab has previously demonstrated[33] that enolizable carbonyl compounds may be deprotonated by weak trialkylamine bases in the presence of suitable magnesium(II)-based Lewis acids to enable highly efficient C–C bond-forming reactions. Excited by the prospect of maintaining aldehyde facial selectivity while suppressing the formation of undesired enone **44**, we imagined assembling polyol **20** by way of a chelate-controlled aldol reaction involving soft enolization with $MgBr_2$•OEt_2.[34] Albeit promising, the reversible nature of soft enolization with magnesium raised new concerns about enolate regioselectivity, substrate dimerization, and aldehyde epimerization. Fortunately, addition of ketone **46a** (1.1 equiv) to aldehyde **47** (1.0 equiv) in the presence of $MgBr_2$•OEt_2 (4.0 equiv) and Hünig base (2.0 equiv) produced the desired aldol adduct **49a** in modest yield and excellent diastereoselectivity (Scheme

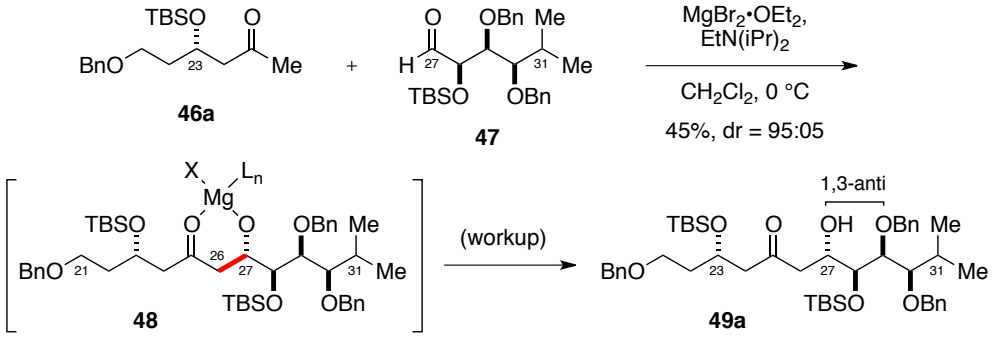
(32) For the earliest examples of magnesium-based soft enolization, see: (a) Rathke, M.W.; Cowan, P.J.; *J. Org. Chem.* **1985**, *50*, 2622–2624; (b) Rathke, M.W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624–2626; (c) Tirpak, R.E.; Olsen, R.S.; Rathke, M.W. *J. Org. Chem.* **1985**, *50*, 4877–4879; (d) Olsen, R.S.; Fataftah, Z.A.; Rathke, M.W. *Synth. Commun.* **1986**, *16*, 1133–1139.

(33) Evans, D.A.; Tedrow, J.S.; Shaw, J.T.; Downey, C.W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393; (b) Evans, D.A.; Downey, C.W.; Shaw, J.T.; Tedrow, J.S. *Org. Lett.* **2002**, *4*, 1127–1130.

(34) For previous examples of direct aldol additions involving soft enolization with $MgBr_2$•OEt_2, see: (a) Wei, H.-X.; Li, K.; Zhang, Q.; Jasoni, R.L.; Hu, J.; Paré, P.W. *Helv. Chim. Acta* **2004**, *87*, 2354–2358; (b) Yost, J.M.; Zhou, G.; Coltart, D.M. *Org. Lett.* **2006**, *8*, 1503–1506; (c) Zhou, G.; Yost, J.M.; Coltart, D.M. *Synthesis* **2007**, 478–482; (d) Yost, J.M.; Alfie, R.J.; Tarsis, E.M.; Chong, I.; Coltart, D.M. *Chem. Commun.* **2011**, *47*, 571–572.

2.9).[28,35] In contrast to the Mukaiyama aldol example (Scheme 2.8), only a trace amount of enone byproduct was formed under these soft enolization conditions. We propose that elimination of the C23 silyloxy substituent is disfavored due to the stability of intermediate magnesium aldolate complex **48**. Furthermore, use of a bulky amine base curtailed aldehyde epimerization[36] while enforcing a desirable level of enolate regioselection.

Scheme 2.9. Model C26–C27 soft enolization-based aldol reaction.



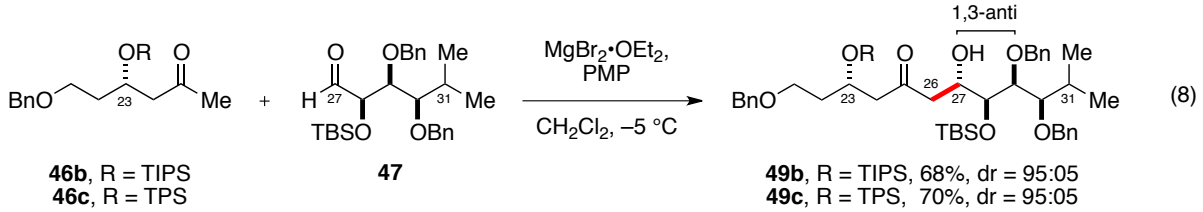
Despite using nearly equimolar amounts of substrate, ketone dimerization[37] posed a formidable challenge to improving reaction yield. We envisioned disfavoring this pathway by enlarging the C23 silyloxy substituent (OTPS, OTIPS > OTBS), and consequently observed increased yields of aldol adducts **49b** and **49c** (eq 8). During the course of our optimization studies, we also noted that increasing the size of the trialkylamine base to PMP (1,2,2,5,5-pentamethylpiperidine) appeared to completely suppress aldehyde epimerization. As before, we used excess base (2.0 equiv) and Lewis acid (4.0 equiv) to reach high conversions over

(35) Reformatsky-type aldol addition of the corresponding a-bromoketone to aldehyde **47** in the presence of SmI_2 in THF at –78 °C also produced the desired aldol adduct **49a** in 85% yield but with slightly diminished diastereoselectivity (dr = 90:10). See: Ref. 20.

(36) In the absence of ketone **46a**, less than 10% epimerization of aldehyde **47** was observed after 0.5 h under the same reaction conditions.

(37) In the absence of aldehyde **47**, complete ketone dimerization was observed within 10 min under the reaction conditions defined in Scheme 2.9.

short reaction times (ca. 6 min at –5 °C),[38] then rapidly quenched the mixtures to avoid decomposition of the desired aldol adducts.



(8)

46b, R = TIPS
46c, R = TPS

47

49b, R = TIPS, 68%, dr = 95:05
49c, R = TPS, 70%, dr = 95:05

Now confident in our ability to construct the C26–C27 bond of polyol **20** using a merged chelate-controlled/soft enolization-based aldol approach, we turned our attention to the syntheses of subunits **35** and **36** (Scheme 2.6).

III. Synthesis of the C3–C26 Ketone[39]

Our synthesis plan for C3–C26 ketone fragment **50** was inspired by the Felkin-selective C15–C16 Mukaiyama aldol reaction that we discovered before the structural revision (Scheme 2.10).[14] We envisioned that trityl-catalyzed[40] addition of the enolsilane of ketone **52** to aldehyde **51** would selectively form the corresponding Felkin aldol adduct despite non-reinforcing α,β-stereoinduction.[41] We anticipated that the same strategy could be used to assemble C16–C26 ketone **52** from aldehyde **55** and Chan's diene[42] (**56**). Finally, we

(38) Temperatures lower than –5 °C significantly limited conversion, even after extended reaction times.

(39) This section represents the culminative work of Drs. William C. Trenkle, Jing Zhang, Joseph M. Young, and Peter H. Fuller.

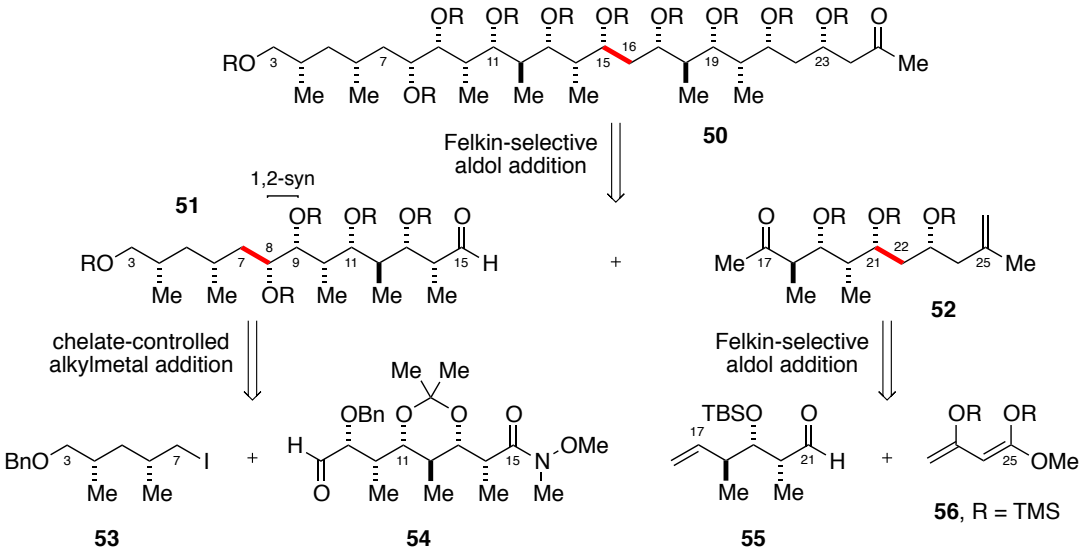
(40) (a) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, *13*, 1759–1762; (b) Denmark, S.E.; Chen, C.-T. *Tetrahedron Lett.* **1994**, *35*, 4327–4330.

(41) Evans, D.A.; Dart, M.J.; Duffy, J.L.; Yang, M.G. *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.

(42) (a) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578–579; (b) Brownbridge, P.; Chan, T.-H.; Brook, M.A.; Kang, G.J. *Can. J. Chem.* **1983**, *61*, 688–693.

expected that chelate-controlled addition[43] of the alkyllithium derivative of iodide **53** to α-alkoxy aldehyde **55** would set the 1,2-syn diol relationship seen in C3–C15 aldehyde **51**.

Scheme 2.10. Retrosynthesis plan for C3–C26 ketone **50**.



A. Synthesis of the C3–C15 Aldehyde

Our synthesis of C3–C15 aldehyde synthon **51** began with the preparation of C3–C7 iodide **53**[44] (Scheme 2.11). The copper-catalyzed, enantioselective hetero-Diels–Alder reaction[45] of enol ether **57**[46] and α-ketoester **58**[47] produced the desired cycloadduct with excellent enantio- and diastereoselection. Substrate-controlled hydrogenation of dihydropyran **60** then afforded the corresponding 1,3-syn dimethyl product as a single diastereomer.

(43) (a) Cram, D.J.; Abd Elhafez, F.A. *J. Am. Chem. Soc.* **1952**, *74*, 5828–5835; (b) Cram, D.J.; Kopecky, K.R. *J. Am. Chem. Soc.* **1959**, *81*, 2748–2755; (c) Cram, D.J.; Leitereg, T.H. *J. Am. Chem. Soc.* **1968**, *90*, 4019–4026.

(44) The synthesis of C3–C7 iodide **53** was previously achieved in 7 steps via a pair of auxiliary-controlled enolate alkylations. See: Vong, B.G.; Abraham, S.; Xiang, A.X.; Theodorakis, E.A. *Org. Lett.* **2003**, *5*, 1617–1620.

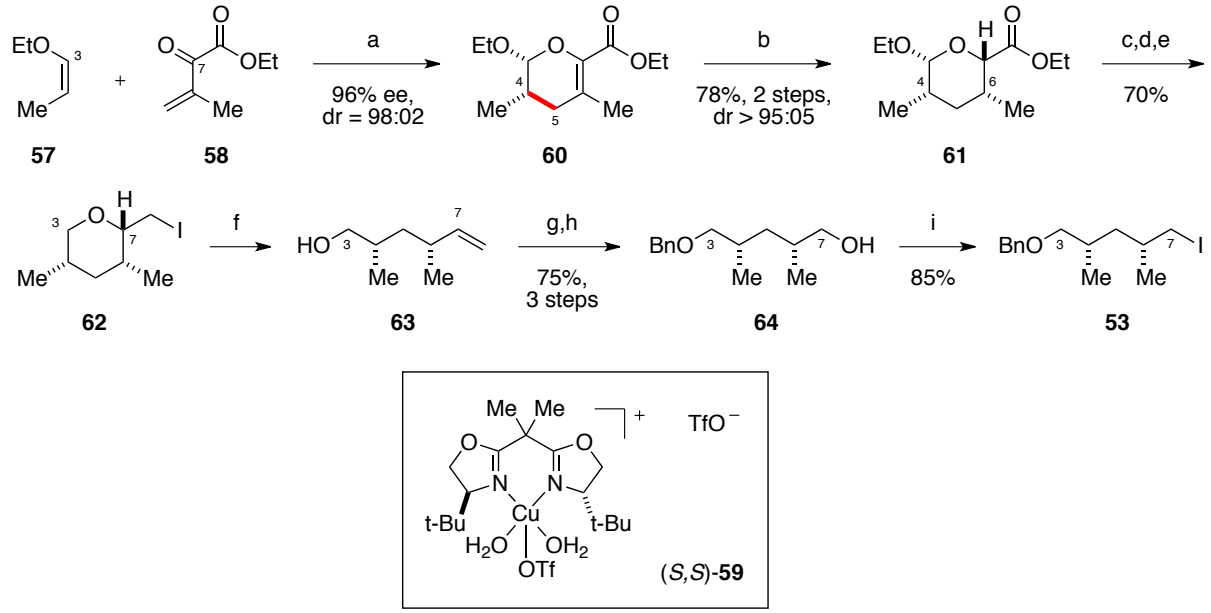
(45) (a) Evans, D.A.; Olhava, E.J.; Johnson, J.S.; Janey, J.M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3372–3375; (b) Evans, D.A.; Johnson, J.S.; Olhava, E.J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.

(46) Prepared in one step by isomerization of allyl ethyl ether. See: Ref. 31 and references cited therein.

(47) Prepared in one step by mono-addition of isopropenylmagnesium bromide to diethyl oxalate. See: (a) Ref. 31; (b) Rambaud, M.; Bakasse, M.; Duguay, G.; Villieras, J. *Synthesis* **1988**, 564–566.

Reduction of ethyl ester **61** and iodination of the resultant primary carbinol proceeded in good yield. Ring fragmentation of iodide **62** was then induced by lithium-halogen exchange to provide acyclic enol **63**.[48] Benzylation, ozonolysis with reductive workup, and iodination ultimately provided C3–C7 iodide **53** in good overall yield and 11 total steps from commercially available material.

Scheme 2.11. Synthesis of C3–C7 iodide **53**.



Reagents and conditions: (a) (*S*,*S*)-**59**, 3 Å MS, Et_2O, –78 °C, 96% ee, dr = 98:02; (b) H_2, Pd/C, EtOAc, rt, dr > 95:05, 78% (2 steps); (c) Et_3SiH, $BF{\bullet}OEt_2$, CH_2Cl_2, –10 °C to 0 °C; (d) $LiAlH_4$, Et_2O, 0 °C; (e) PPh_3, I_2, imidazole, MeCN, PhH, 55 °C, 70% (3 steps); (f) *t*-BuLi, Et_2O, –78 °C; (g) BnBr, NaH, DMF, 0 °C; (h) O_3, Na_2CO_3, Sudan III, EtOH, CH_2Cl_2, –78 °C; $NaBH_4$, –78 °C to rt, 75% (3 steps); (i) PPh_3, I_2, imidazole, CH_2Cl_2, 0 °C to rt, 85%.

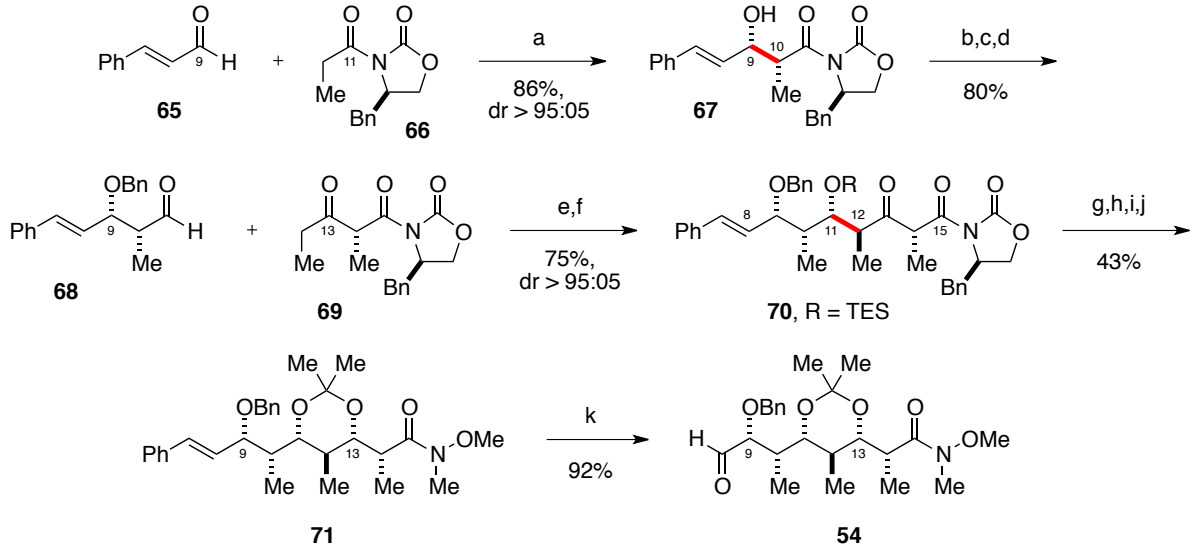
Our synthesis of the C3–C15 aldehyde continued with the preparation of C8–C15 aldehyde **54** (Scheme 2.12). The syn aldol reaction of cinnamaldehyde (**65**) and oxazolidinone **66** produced the desired adduct in very good yield and excellent diastereoselectivity.[49] Benzylation of the C9 carbinol and net reduction of imide **67** to its corresponding aldehyde

(48) The catalytic, enantioselective synthesis of **ent-63** was previously developed by our group and applied to the synthesis of (+)-azaspiracid-1. See: (a) Evans, D.A.; Dunn, T.B.; Kvœrnø, L.; Beauchemin, A.; Raymer, B.; Olhava, E.J.; Mulder, J.A.; Juhl, M.; Kagechika, K.; Favor, D.A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4698–4703; (b) Ref. 29.; (c). Ref. 31.

(49) Evans, D.A.; Bartroli, J.; Shih, T.L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

proceeded in very good yield. Boron-mediated aldol addition of β-ketoimide **69**[50] to aldehyde **68** was immediately followed by silylation of the nascent C11 carbinol to produce adduct **70** in good yield and excellent diastereoselectivity. Diastereoselective reduction of the C13 carbonyl with zinc borohydride gave the desired anti/anti/syn C11–C14 stereotetrad with excellent selectivity.[51] Transamidation of the intermediate imide, acetonide formation, and ozonolysis of styryl derivative **71** completed the synthesis of C8–C15 aldehyde **54** in 11 linear steps and very good overall yield.

Scheme 2.12. Synthesis of C8–C15 aldehyde **54**.



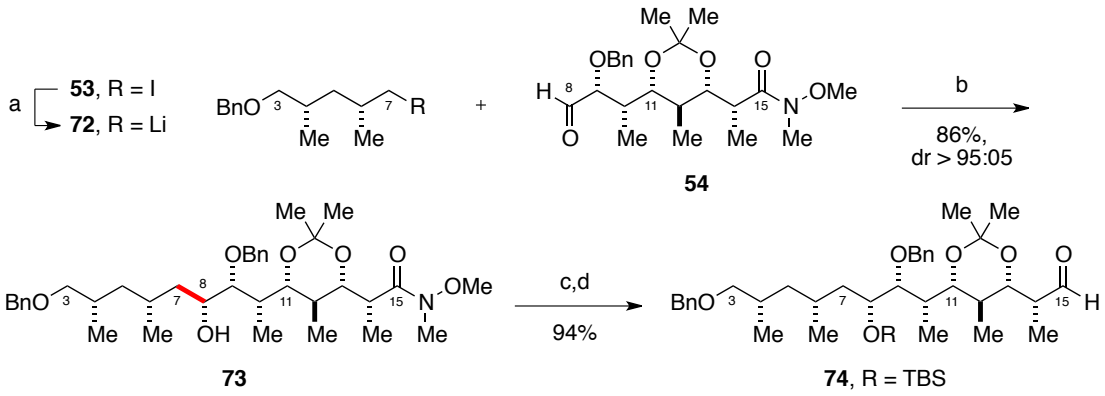
Reagents and conditions: (a) Bu_2BOTf, Et_3N, CH_2Cl_2, –78 °C to 0 °C, dr > 95:05, 86%; (b) Me(MeO)NH•HCl, $AlMe_3$, THF, –78 °C, 87%; (c) BnBr, NaH, DMF, –10 °C, 99%; (d) $LiAlH_4$, Et_2O, 0 °C to rt, 93%; (e) Cy_2BCl, $EtNMe_2$, Et_2O, –78 °C, dr > 95:05; (f) TESOTf, 2,6-lut., CH_2Cl_2, –78 °C, 75% (2 steps); (g) $Zn(BH_4)_2$, Et_2O, CH_2Cl_2, –55 °C to –25 °C, 59%; (h) Me(MeO)NH•HCl, $AlMe_3$, THF, –78 °C to 0 °C, 80%; (i) AcOH, THF, H_2O, rt; (j) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt, 91% (2 steps); (k) O_3, py, Sudan III, EtOH, CH_2Cl_2, –78 °C; Me_2S, –78 °C to rt, 92%.

(50) Evans, D.A.; Ng, H.P.; Clark, J.S.; Rieger, D.L. *Tetrahedron* **1992**, *48*, 2127–2142.

(51) (a) Halstead, D.P. *Total Syntheses of Miyakolide & Discodermolide*. Ph.D. Thesis, Harvard University, **1998**; (b) Nakata, T.; Oishi, T. *Tetrahedron Lett*. **1980**, *21*, 1641–1644; (c) Nakata, T.; Oishi, T. *Acc. Chem. Res*. **1984**, *17*, 338–344.

Our synthesis of C3–C15 aldehyde **74** concluded with union of the C3–C7 and C8–C15 fragments (Scheme 2.13).[52] Chelate-controlled addition of alkyllithium **72** to α-alkoxy aldehyde **54** yielded the desired 1,2-syn diol derivative **73** as a single diastereomer in very good yield. Silylation of the C8 carbinol and reduction of the Weinreb amide produced C3–C15 aldehyde **74** in excellent yield and overall convergency (14 longest linear steps, 25 overall).

Scheme 2.13. Synthesis of C3–C15 aldehyde **74**.



Reagents and conditions: (a) *t*-BuLi, Et_2O, pentane, –78 °C; (b) $MgBr_2$•OEt_2, CH_2Cl_2, –78 °C, dr > 95:05, 86%; (c) TBSOTf, 2,6-lut., CH_2Cl_2, –78 °C to 0 °C, 97%; (d) $LiAlH_4$, Et_2O, 0 °C, 97%.

B. Syntheses of the C16–C26 Enolsilane and C3–C26 Ketone

Our synthesis of C3–C26 ketone synthon **50** continued with the preparation of the enolsilane of C16–C26 ketone synthon **52**[53] via C16–C21 aldehyde **55**[54] (Scheme 2.14). Syn aldol reaction[55] of methacrolein (**75**) and oxazolidinone **66** was followed by silylation of the nascent C19 carbinol to produce adduct **76** in very good yield and excellent

(52) This reaction sequence was performed by Dr. Peter H. Fuller. The synthesis of the corresponding C3 TBS ether of C3–C15 aldehyde **74** was achieved by Dr. Joseph M. Young. See: Ref. 14.

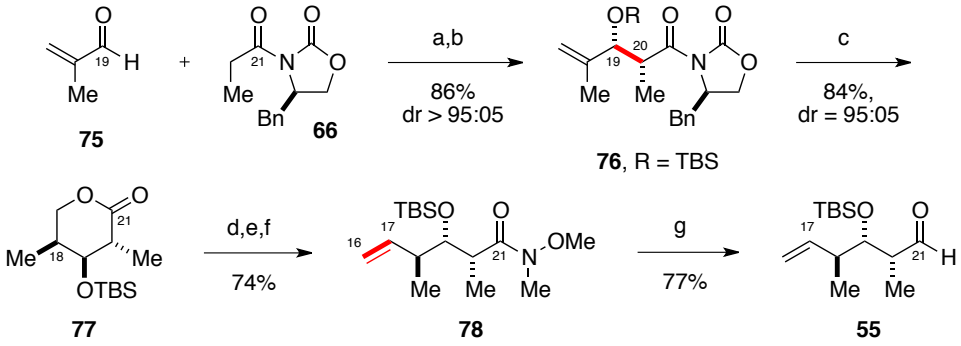
(53) The synthesis of C16–C26 enolsilane **83** (*vide infra*) was previously achieved by Dr. Joseph M. Young in 13 steps via a pair of auxiliary-controlled aldol reactions. See: Ref 14.

(54) The synthesis of C16–C21 aldehyde **55** in 7 steps from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate was previously reported. See: Mínguez, J.M.; Kim, S.-Y.; Giuliano, K.A.; Balachandran, R.; Madiraju, C.; Day, B.W.; Curran, D.P. *Bioorg. Med. Chem.* **2003**, *11*, 3335–3357.

(55) Evans, D.A.; Fitch, D.M. *J. Org. Chem.* **1997**, *62*, 454–455.

diastereoselectivity. Substrate-controlled hydroboration[56] selectively established the C18 methyl stereocenter and afforded γ-lactone **77** in very good yield upon oxidative workup. Oxidative ring opening, C16–C17 olefination, and reduction of Weinreb amide **78** gave aldehyde **55** in good overall yield.

Scheme 2.14. Synthesis of C16–C21 aldehyde **55**.



Reagents and conditions: (a) Bu_2BOTf, $EtN(iPr)_2$, –78 °C to 0 °C, dr > 95:05, 88%; (b) TBSOTf, 2,6-lut., CH_2Cl_2, –78 °C to –20 °C, 98%; (c) 9-BBN, THF, 0 °C; aq H_2O_2, pH 7 buffer, EtOH, 0°C to rt; cat. KO*t*-Bu, THF, 0 °C to rt, dr = 95:05, 84%; (d) Me(MeO)NH•HCl, $AlMe_3$, THF, –40 °C to 0 °C; (e) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to 0 °C; (f) $Ph_3PPMeBr$, NaHMDS, THF, –78 °C to 0 °C, 74% (3 steps); (g) DIBALH, CH_2Cl_2, –78 °C, 77%.

The synthesis of C16–C26 enolsilane **83**[57] continued with the trityl-catalyzed[40] addition of Chan's diene[42] (**56**) to C16–C21 aldehyde **55** to form Felkin aldol adduct **79** in very good yield and excellent diastereoselectivity (Scheme 2.15). Prasad 1,3-syn reduction[58] was followed by cerium-mediated conversion of ester **80** to its corresponding allylsilane[59] and global desilylation to produce triol **81** in good yield. Selective protection of the C23 carbinol

(56) (a) Still, W.C.; Barrish, J.C. *J. Am. Chem. Soc.* **1983**, *105*, 2487–2489; (b) Midland, M.M.; Kwon, Y.C. *J. Am. Chem. Soc.* **1983**, *105*, 3725–3727.

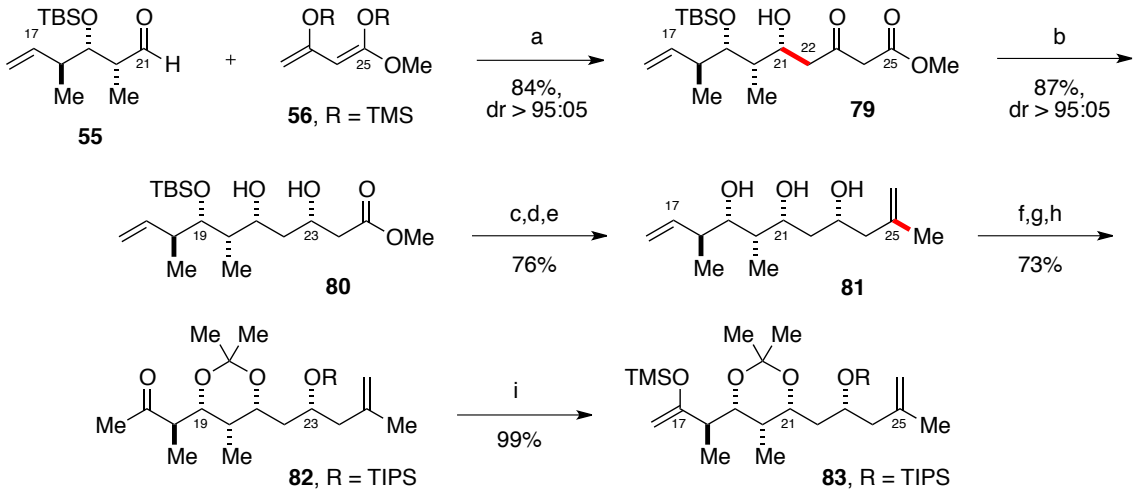
(57) The synthesis of C16–C26 enolsilane **83** from methyl ester **80** was designed in collaboration with Dr. Peter H. Fuller, and executed by Dr. Fuller.

(58) Chen, K.-M.; Hardtmann, G.E.; Prasad, K.; Repič, O; Shapiro, M.J. *Tetrahedron Lett.* **1987**, *28*, 155–158.

(59) (a) Anderson, M.B.; Fuchs, P.L. *Synth. Commun.* **1987**, *17*, 621–635; (b) Narayanan, B.A.; Bunnelle, W.H. *Tetrahedron Lett.* **1987**, *28*, 6261–6264; (c) Lee, T.V.; Channon, J.A.; Cregg, C.; Porter, J.R.; Roden, F.S.; Yeoh, H.T.-L. *Tetrahedron* **1989**, *45*, 5877–5886; (d) Bunnelle, W.H.; Narayanan, B.A. *Org. Synth.* **1990**, *69*, 89–92; *Org. Synth.* **1993**, *Coll. Vol. 8*, 602–605.

as its triisopropylsilyl ether, 1,3-syn acetonide formation and Wacker oxidation[60] of the C16–C17 alkene produced methyl ketone **82** in good overall yield and 15 linear steps. The synthesis was capped by formation of enolsilane **83** in preparation for the C15–C16 Mukaiyama aldol reaction.

Scheme 2.15. Synthesis of C16–C26 enolsilane **83**.

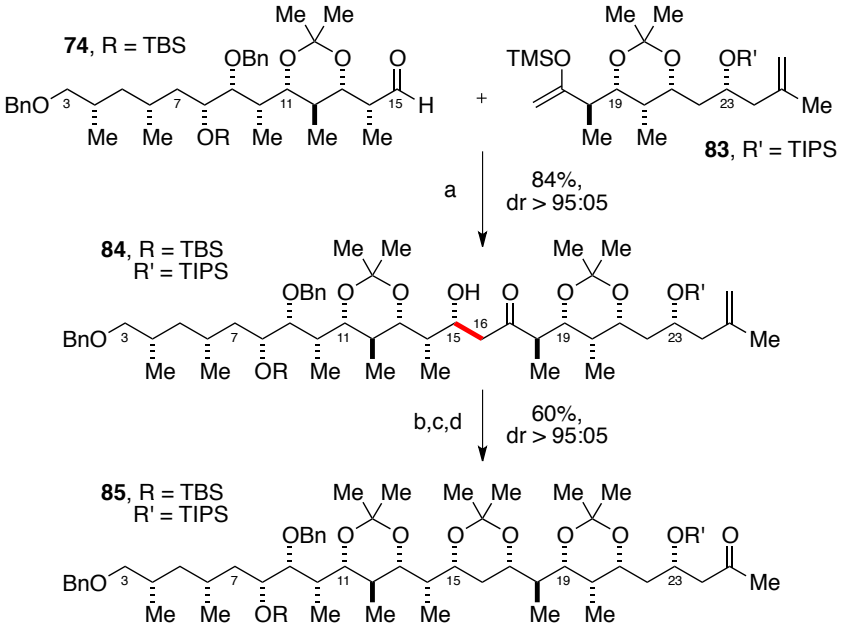


Reagents and conditions: (a) Ph_3PCPF_6 (5 mol%), CH_2Cl_2, –78 °C; PPTS, MeOH, 0 °C to rt, dr > 95:05, 84%; (b) Et_2BOMe, $NaBH_4$, THF, MeOH, –78 °C to –50 °C; aq H_2O_2, pH 7 buffer, MeOH, –50 °C to rt, dr > 95:05, 87%; (c) TMSOTf, 2,6-lut., CH_2Cl_2, –78 °C to rt; (d) $TMSCH_2MgBr$, $CeCl_3$, THF, Et_2O, –78 °C to rt; (e) HF•py, CH_2Cl_2, 0 °C to rt, 76% (3 steps); (f) TIPSCl, imidazole, DMF, rt to 45 °C, 91%; (g) $Me_2C(OMe)_2$, PPTS, acetone, rt, 93%; (h) $PdCl_2$(quinox), $AgSbF_6$, aq *t*-BuOOH, CH_2Cl_2, 0 °C to rt, 86%; (i) TMSOTf, Et_3N, CH_2Cl_2, –78 °C to –20 °C, 99%.

Our synthesis of C3–C26 ketone **85** concluded with merging of the C3–C15 and C16–C26 fragments (Scheme 2.16). Encouraged by results obtained before the structural revision, the trityl-catalyzed[40] addition of enolsilane **83** to aldehyde **74** proceeded in similar fashion to produce the desired Felkin aldol adduct **84** as a single C15 diastereomer in very good yield. Prasad 1,3-syn reduction[58] was followed by acetonide formation and ozonolysis to provide C3–C26 ketone **85** in good overall yield and 20 linear steps.

(60) Michel, B.W.; Camelio, A.M.; Cornell, C.N.; Sigman, M.S. *J. Am. Chem. Soc.* **2009**, *131*, 6076–6077.

Scheme 2.16. Synthesis of C3–C26 ketone **85**.



Reagents and conditions: (a) Ph_3PCPF_6 (3 x 10 mol%), CH_2Cl_2, –78 °C; PPTS, MeOH, 0 °C, dr > 95:05, 84%; (b) Et_2BOMe, $NaBH_4$, THF, MeOH, –78 °C to –20 °C; aq H_2O_2, pH 7 buffer, MeOH, –20 °C to rt, dr > 95:05, 87%; (c) $Me_2C(OMe)_2$, PPTS, acetone, rt, 85%; (d) O_3, py, EtOH, CH_2Cl_2, –78 °C; Me_2S, –78 °C to rt, 81%.

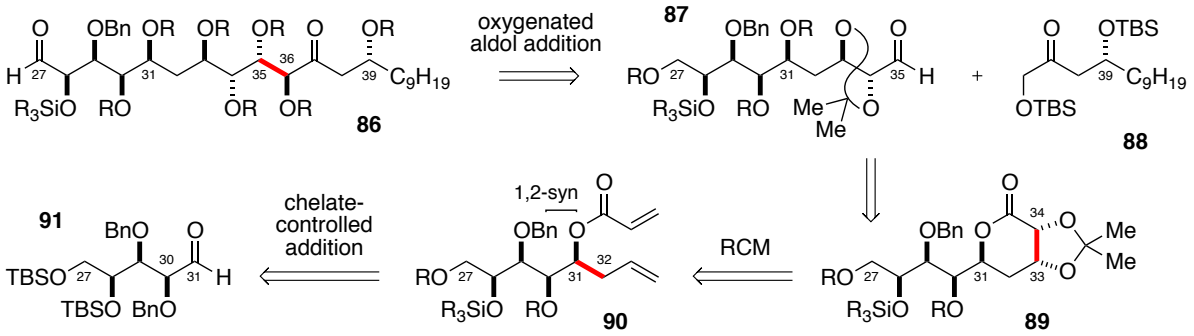
IV. Synthesis of the C27–C48 Aldehyde[61]

Our synthesis plan for C27–C48 aldehyde fragment **86** was designed to take advantage of the anti-Felkin selective α-oxygenated aldol reaction developed specifically for the C33–C36 stereochemical array (Scheme 2.17).[62] We presumed that the intervening structural revision would have minimal impact on reaction diastereoselectivity, and therefore decided to target the same C35–C36 aldol bond disconnection. This act produced C36–C48 ketone **88** and C27–C35 aldehyde **87**, the latter of which could be accessed stereoselectively from C27–C31 aldehyde **91** via a series of allylation, ring-closing metathesis and dihydroxylation steps.

(61) The synthesis of C27–C48 aldehyde **117** was designed and performed by the author in collaboration with Dr. Egmont Kattnig.

(62) (a) Glorius, F. *Development of α-Oxygenated Aldol Methodology and Progress Towards the Synthesis of Aflastatin A*. Postdoctoral Report, Harvard University, **2001**; (b) Evans, D.A.; Glorius, F.; Burch, J.D. *Org. Lett*. **2005**, *7*, 3331–3335.

Scheme 2.17. Retrosynthesis plan for C27–C48 aldehyde **86**.



Two syntheses of C36–C48 ketone **88** were achieved before the structural revision (Scheme 2.18). The first route[62a] featured the copper-catalyzed, enantioselective aldol addition of silylketene acetal **93** to benzyloxy acetaldehyde (**92**).[63] The resulting absolute stereochemistry of the C37 carbinol was then relayed to C39 by Evans-Tishchenko 1,3-anti reduction,[64] and ultimately produced gram-scale quantities of ketone **88** in 9 steps, 46% overall yield and 98% ee. A shorter, second route[65] was based upon the enantioselective methallylation[66] of decanal, providing the desired fragment in 6 steps, 36% unoptimized overall yield and 96% ee.

Our synthesis of the C27–C48 aldehyde began with the preparation of C27–C31 aldehyde **91** from methyl α-D-(+)-glucopyranoside (**99**) (Scheme 2.19). Regioselective dibenzylation,[67] iodination[68] and silylation produced pyranoside **101** in good overall yield.

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(63) (a) Evans, D.A.; Murry, J.A.; Kozlowski, M.C. *J. Am. Chem. Soc.* **1996**, *118*, 5814–5815; (b) Evans, D.A.; Kozlowski, M.C.; Murry, J.A.; Burgey, C.S.; Campos, K.R.; Connell, B.T.; Staples, R.J. *J. Am. Chem. Soc.* **1999**, *121*, 669–685; (c) Allison, B.D. *Chelate Control: A Pivotal Design Element in Asymmetric Synthesis*. Ph.D. Thesis, Harvard University, **2001**.

(64) Evans, D.A.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.

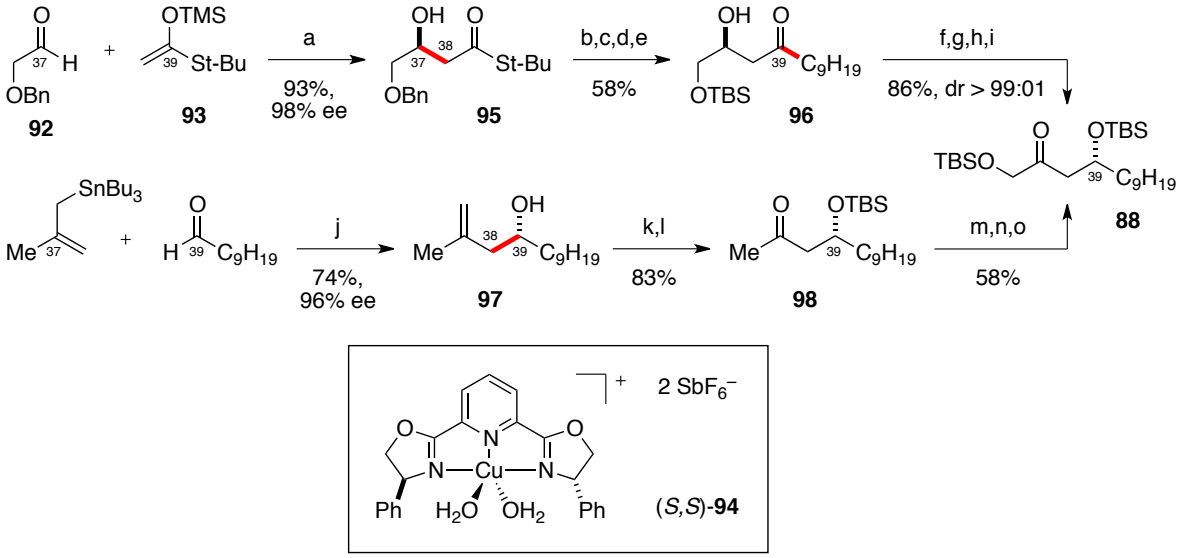
(65) Thaisrivongs, D.A. *Synthesis of the C5'–C2 and C36–C48 Subunits of Aflastatin A*. A.B. Thesis, Harvard University, **2007**.

(66) (a) Keck, G.E.; Tarbet, K.H.; Geraci, L.S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468; (b) Keck, G.E.; Krishnamurthy, D.; Grier, M.C. *J. Org. Chem.* **1993**, *58*, 6543–6544; (c) Keck, G.E.; Krishnamurthy, D. *Org. Synth.* **1998**, *75*, 12–18.

(67) Français, A.; Urban, D.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8662–8665.

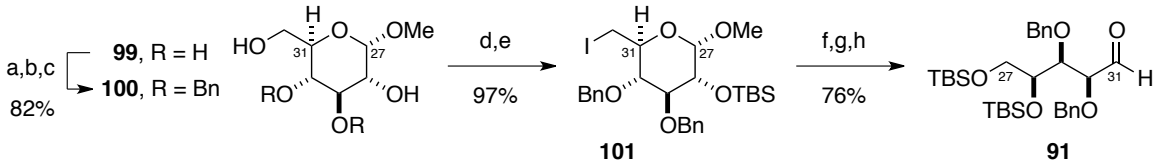
Zinc-mediated fragmentation[69] and *in situ* reduction produced an intermediate enol that was silylated and oxidatively cleaved, ultimately furnishing C27–C31 aldehyde **91** in eight steps and 52% overall yield.

Scheme 2.18. Previous syntheses of C36–C48 ketone **88**.



Reagents and conditions: (a) (*S*,*S*)-**94**, CH_2Cl_2, –78 °C; aq HCl, THF, rt, 93%, 98% ee; (b) Me(MeO)NH•HCl, $AlMe_3$, THF, –15 °C to rt, 97%; (c) Pd/C, H_2, EtOAc, rt, 98%; (d) TBSCl, imidazole, THF, CH_2Cl_2, 0 °C, 92%; (e) $C_9H_{19}MgBr$, THF, 0 °C to rt, 66%; (f) SmI_2, iPrCHO, THF, –10 °C, dr > 99:01, 91%; (g) TBSOTf, 2,6-lut., CH_2Cl_2, 0 °C, 99%; (h) DIBALH, PhMe, –78 °C, 97%; SO_3•Py, Et_3N, DMSO, CH_2Cl_2, –55 °C to 0 °C, 98%; (j) (*S*)-(–)-1,1'-bi-2-naphthol, $Ti(OiPr)_4$, 4 Å MS, CH_2Cl_2, –78 °C to –20 °C, 74%, 96% ee; (k) TBSCl, imidazole, DMF, rt, 83%; (l) O_3, py, CH_2Cl_2, MeOH, –78 °C; Me_2S, –78 °C to rt, quant.; (m) LDA, THF; TMSCl, Et_3N, –78 °C to rt; (n) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt; aq HCl, THF, H_2O, rt; (o) TBSCl, imidazole, DMF, rt to 50 °C, 58% (3 steps).

Scheme 2.19. Synthesis of C27–C31 aldehyde **91**.



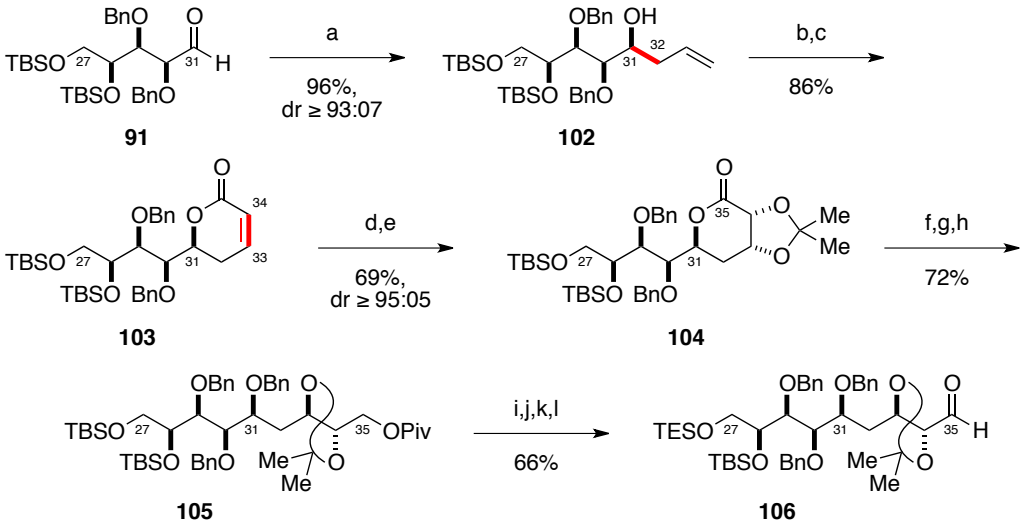
Reagents and conditions: (a) TMSCl, py, CH_2Cl_2, 0 °C to rt, quant.; (b) PhCHO, $Cu(OTf)_2$, CH_2Cl_2, MeCN; Et_3SiH, 0 °C to rt; (c) BH_3•THF, $Cu(OTf)_2$, 82% (2 steps); (d) PPh_3, I_2, imidazole, PhMe, MeCN, rt, 97%; (e) TBSCl, imidazole, CH_2Cl_2, 0 °C to rt, quant.; (f) Zn, THF, H_2O,))), 45 °C; $NaBH_4$, 0 °C, 88%; (g) TBSCl, imidazole, CH_2Cl_2, 0 °C to rt, 92%; (h) O_3, py, CH_2Cl_2, MeOH, –78 °C; PPh_3, –78 °C to rt, 94%.

(68) (a) Garegg, P.J.; Samuellson, B. *J. Chem. Soc., Perkin Trans. I.* **1980**, 2866–2869; (b) Garegg, P.J.; Johansson, R.; Ortega, C.; Samuellson, B. *J. Chem. Soc., Perkin Trans. I.* **1982**, 681–683.

(69) Skaanderup, P.R.; Hyldtoft, L.; Madsen, R. *Monatsh. Chem.* **2002**, *133*, 467–472.

Our synthesis of the C27–C48 aldehyde continued with the stereoselective allylation of syn α,β-bisalkoxy aldehyde **91** (Scheme 2.20). Although both α- and β-oxygen substituents were available for chelation,[70] the rate of reaction of allylmagnesium bromide with the five-membered chelate[43] was significantly faster,[71] producing homoallylic alcohol **102** in 96% yield and excellent diastereoselectivity (dr ≥ 93:07). We observed that the nature of the nucleophile[20,24] and distal carbinol protecting groups (at C27 and C28)[20] were important for maintaining excellent diastereoselection.

Scheme 2.20. Synthesis of C27–C35 aldehyde **106**.



Reagents and conditions: (a) $MgBr_2$•OEt_2, allylMgBr, CH_2Cl_2, Et_2O, PhMe, –78 °C, 96%, dr ≥ 93:07; (b) acrylic pivalic anhydride, $EtN(iPr)_2$, DMAP, THF, PhH, rt, 94%; (c) $(Ph_3P)_2Cl_2Ru$=CHPh, PhH, 65 °C, 92%; (d) $RuCl_3$, $CeCl_3$•$7H_2O$, $NaIO_4$, EtOAc, MeCN, H_2O, 0 °C, dr ≥ 95:05; (e) $Me_2C(OMe)_2$, PPTS, acetone, 30 °C, 69% (2 steps); (f) $LiBH_4$, THF, H_2O, 0 °C to rt; (g) PivCl, py, 0 °C to rt, 78% (2 steps); (h) BnBr, NaH, nBu_4NI, THF, 0 °C to rt, 92%; (i) HF•py, py, THF, 0 °C to rt, 85%; (j) TESOTf, 2,6-lut., CH_2Cl_2, 0 °C, 91%; (k) DIBALH, CH_2Cl_2, PhMe, –78 °C, 90%; (l) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C, 95%.

(70) The possibility of bicyclic chelates involving the aldehyde carbonyl and both oxygen substituents cannot be ruled out. See: (a) Charette, A.B.; Mellon C.; Rouillard, L.; Malenfant, E. *Pure Appl. Chem.* **1992**, *64*, 1925–1931; (b) Charette, A.B.; Mellon C.; Rouillard, L.; Malenfant, E. *Synlett* **1993**, 81–82.

(71) For examples that suggest five-membered magnesium chelates react much faster than six-membered chelates, see: (a) Frye, S.V.; Eliel, E.L.; Cloux, R. *J. Am. Chem. Soc.* **1987**, *109*, 1862–1863; (b) Williams, D.R.; Klingler, F.D. *Tetrahedron Lett.* **1987**, *28*, 869–872; (c) Keck, G.E.; Andrus, M.B.; Romer, D.R. *J. Org. Chem.* **1991**, *56*, 417–420; (d) Burgess, K.; Chaplin, D.A. *Tetrahedron Lett.* **1992**, *33*, 6077–6080.

Acryloylation[72] of the nascent C31 carbinol, and ring-closing metathesis[73] of the intermediate diene then furnished unsaturated lactone **103**. Stereoselective dihydroxylation[74,75] and acetonide formation produced lactone **104** as a single diastereomer. Reduction to the diol, selective protection of the primary carbinol, and benzylation yielded pivalate ester **105**. Silyl protecting group exchange at C27 was necessary at this stage because selective removal of the TBS ether[76] after C35–C36 aldol coupling would later prove difficult. Reductive removal of the ester and Parikh-Doering oxidation[77] ultimately provided C27–C35 aldehyde **106** in 12 steps and 27% overall yield from aldehyde **91**.

With scalable routes to C36–C48 ketone **88** and C27–C35 aldehyde **106** in hand, the synthesis of the C27–C48 fragment was nearly complete. At this juncture, it was unclear how the revised stereochemistry (C28–C31) of aldehyde **106** would influence the diastereoselectivity of our planned C35–C36 aldol reaction. Addition of the corresponding (*E*) enolate of ketone **88** to this aldehyde produced the desired anti-Felkin product **107** in fairly good isolated yield but with unexpectedly diminished diastereoselection (Scheme 2.21, eq 9). A similar result was observed for an aldehyde (**108**) having the same relative configuration between C31 and C33 (Scheme 2.21, eq 10).[20] Both examples deviated from the good yields

(72) Tanaka, A.; Suzuki, H.; Yamashita, K. *Agric. Biol. Chem.* **1989**, *53*, 2253–2256.

(73) Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R.H. *Angew. Chem.* **1995**, *107*, 2179–2181; *Angew. Chem., Int. Ed.* **1995**, *34*, 2039–2041.

(74) (a) Plietker, B.; Niggemann, M. *J. Org. Chem.* **2005**, *70*, 2402–2405; (b) Plietker, B. *Synthesis* **2005**, 2453–2472.

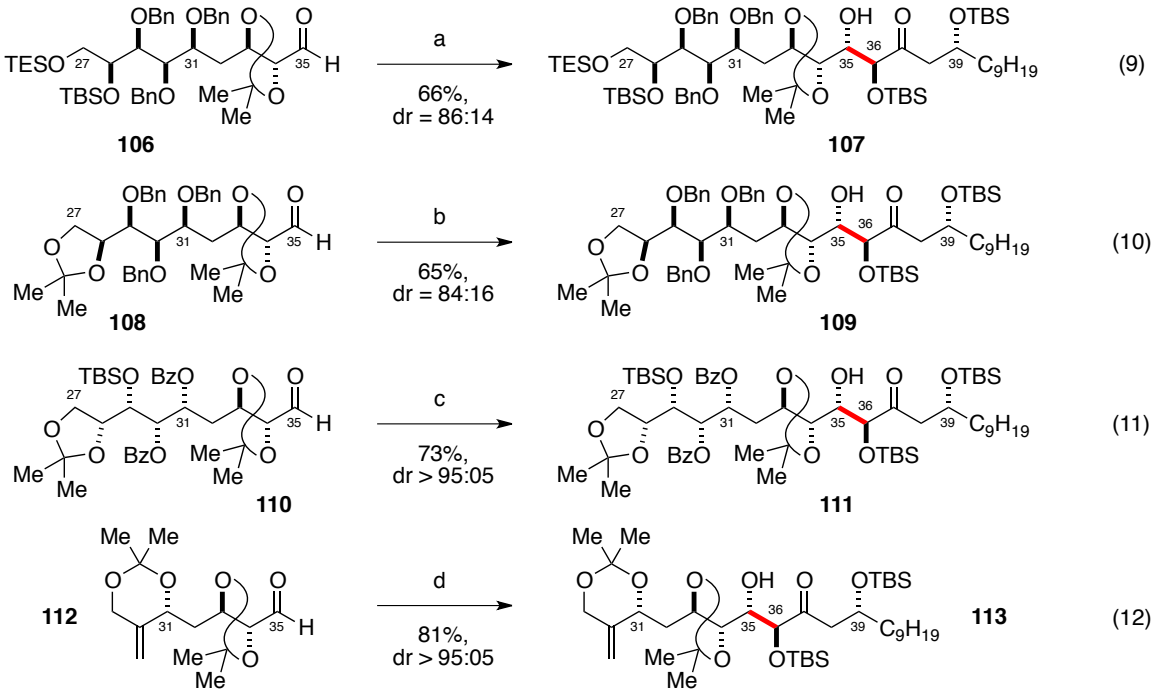
(75) For examples of the diastereoselective dihydroxylation of related α,β-unsaturated δ-lactones using Upjohn conditions (OsO_4, NMO), see: (a) Ghosh, A.K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 3967–3969; (b) Ramachandran, P.V.; Prabhudas, B.; Chandra, J.S.; Reddy, M.V.R. *J. Org. Chem.* **2004**, *69*, 6294–6304; (c) Bhaket, P.; Stauffer, C.S.; Datta, A. *J. Org. Chem.* **2004**, *69*, 8594–8601.

(76) Selective desilylation of the C27 carbinol was achieved under specific buffered conditions. See: Hu, T.; Takenaka, N.; Panek, J.S. *J. Am. Chem. Soc.* **2002**, *124*, 12806–12815.

(77) Parikh, J.R.; Doering, W.v.E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

and excellent diastereoselectivities obtained prior to the C28–C31 stereochemical revision (Scheme 2.21, eqs 11,12).[7,15]

Scheme 2.21. C35–C36 oxygenated aldol reactions.



Reagents and conditions: (a) ketone **88**, Cy_2BCl, Me_2NEt, pentane, 0 °C to rt; aldehyde **106**, pentane, PhMe, –78 °C to –20 °C, 66%, dr = 86:14; (b) ketone **88**, Cy_2BCl, Me_2NEt, pentane, 0 °C to rt; aldehyde **108**, pentane, PhMe, –78 °C to –20 °C, 65%, dr = 84:16; (c) ketone **88**, Cy_2BCl, Me_2NEt, pentane, 0 °C to rt; aldehyde **110**, pentane, PhMe, –78 °C to –20 °C, 73%, dr > 95:05; (d) ketone **88**, Cy_2BCl, Me_2NEt, pentane, 0 °C to rt; aldehyde **112**, pentane, –78 °C to –20 °C, 81%, dr > 95:05.

The reduced diastereoselection for the anti-Felkin product may be attributed to the inversion of relative configuration between the C31 and C33 carbinol stereocenters. When these stereocenters exist in a 1,3-anti relationship, anti-Felkin transition state **114** benefits both from dipole-dipole minimization and extension of the aldehyde's alkyl chain away from the reaction center (Figure 2.1A). When this relationship is inverted, the transition states (**115**–**117**) that lead to desired anti-Felkin products **107** and **109** become destabilized by unfavorable steric and/or electrostatic interactions, regardless of C31–C32 rotational isomer (Figure 2.1B).

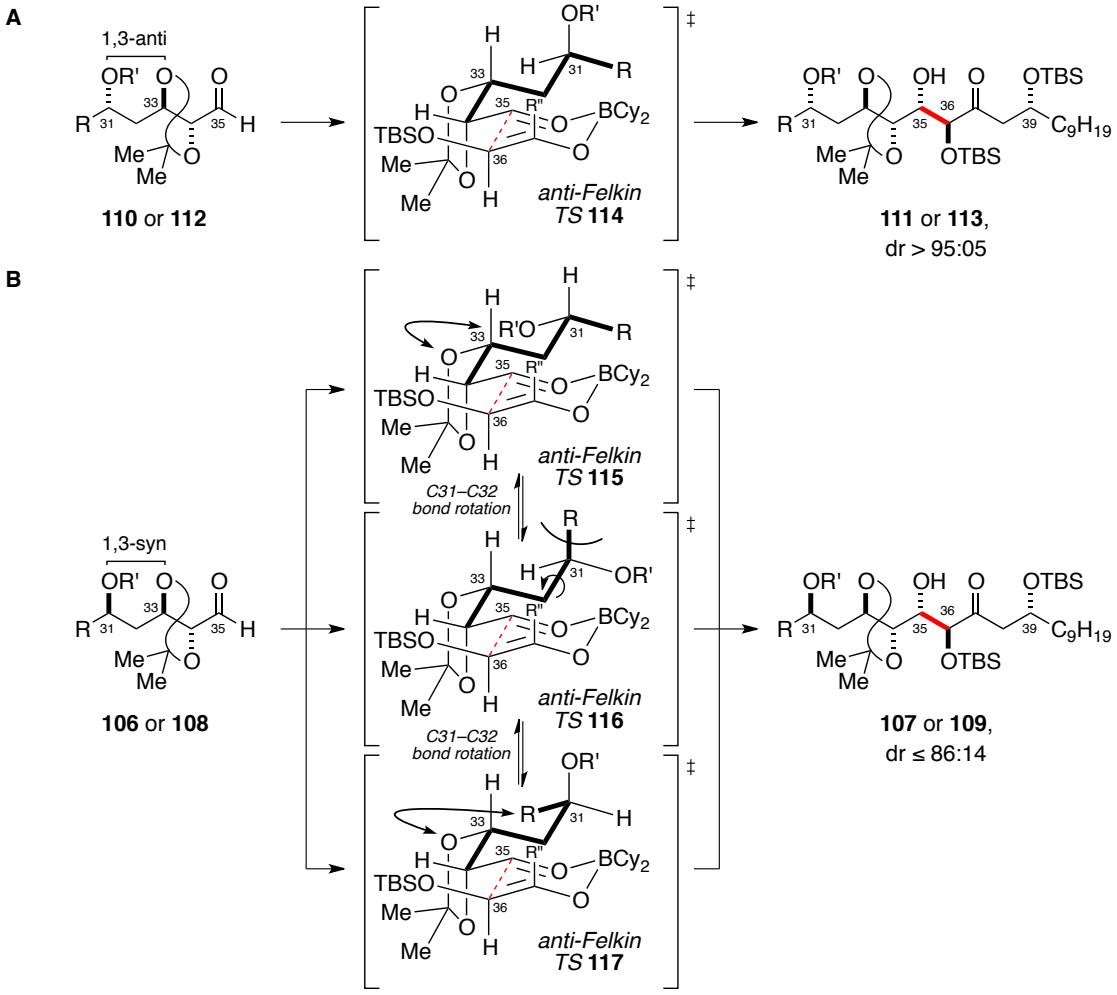
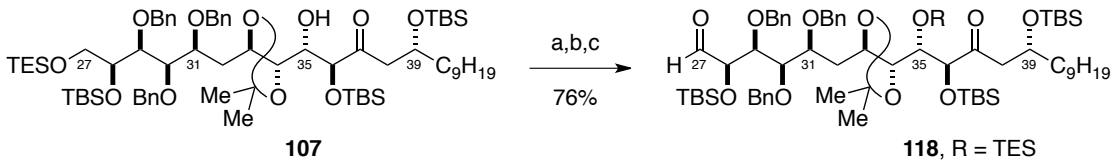


Figure 2.1. C35–C36 oxygenated aldol anti-Felkin transition state possibilities.

Our synthesis of C27–C48 aldehyde **118** was completed in short order (Scheme 2.22). Silylation of aldol adduct **107** was followed by selective deprotection and oxidation[77] at C27. This sequence provided C27–C48 fragment **118** in good overall yield and 24 linear steps.

Scheme 2.22. Synthesis of C27–C48 aldehyde **118**.



Reagents and conditions: (a) TESOTf, 2,6-lut., CH_2Cl_2, 0 °C, 87%; (b) PPTS, CH_2Cl_2, MeOH, 0 °C to rt, quant.; (c) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C, 87%.

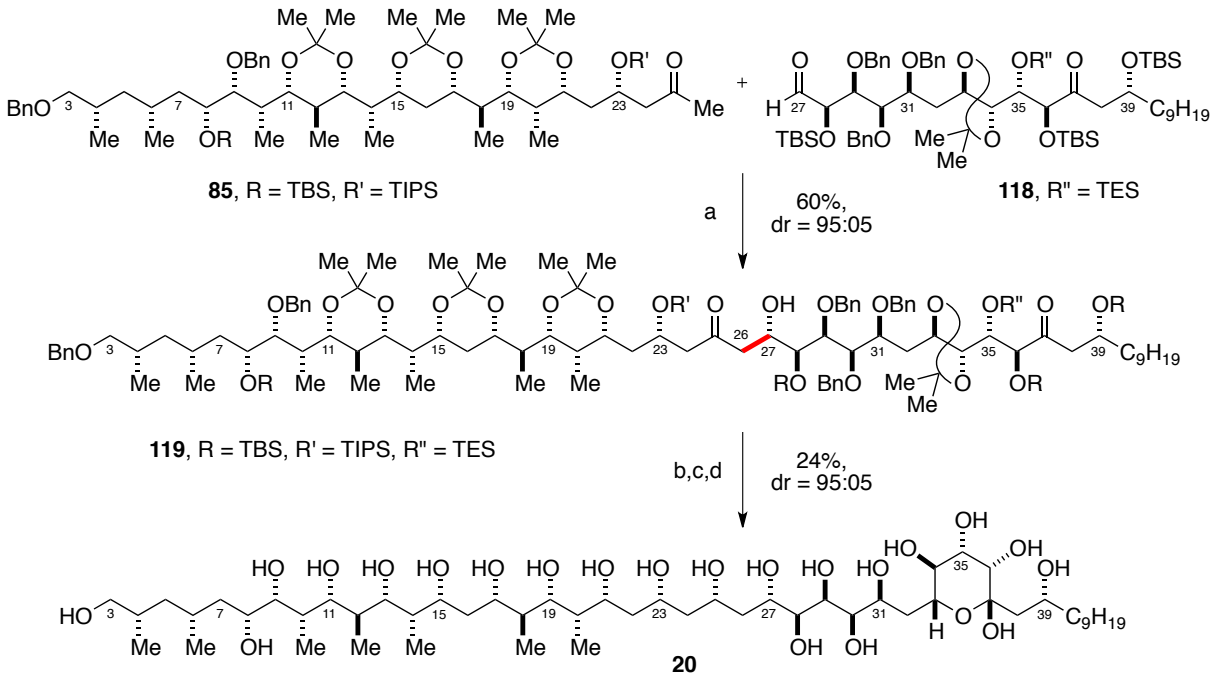
V. Synthesis of the C3–C48 Degradation Fragment[78]

Having completed the syntheses of both the C3–C26 and C27–C48 fragments, we ventured forward with the key aldol coupling (Scheme 2.23).[20] Satisfyingly, chelate-controlled addition of ketone **85** to aldehyde **118** under our soft enolization conditions delivered the desired β-hydroxy ketone **119** with excellent diastereoselection.[28] We reduced the aldol adduct under Prasad's conditions[58] to afford the corresponding 1,3-syn diol in good yield. Both steps were completely chemoselective and eliminated the need to mask the C37 carbonyl. To conclude the synthesis of the target structure, the intermediate diol was subjected to a two-step deprotection sequence. We found that removal of the acetonide and silyl protecting groups was best achieved with hexafluorosilicic acid,[79] but noted that removal of the C36 TBS ether was particularly troublesome and limited yield. Deprotection over longer reaction times, with larger excess reagent, or with resubjection of incompletely deprotected material to the original reaction conditions increased overall conversion at the cost of decomposition. Ultimately, the remaining benzyl ethers were cleaved to unveil C3–C48 degradation fragment **20** in modest overall yield and 28 linear steps.

(78) The synthesis of C3–C48 degradation fragment **20** was first performed by Dr. Egmont Kattnig in collaboration with Dr. Peter H. Fuller and the author.

(79) (a) Pilcher, A.S.; Hill, D.K.; Shimshock, S.J.; Waltermire, R.E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492–2495; (b) Pilcher, A.S.; Shimshock, S.J. *J. Org. Chem.* **1993**, *58*, 5130–5134.

Scheme 2.23. Synthesis of C3–C48 degradation fragment **20**.

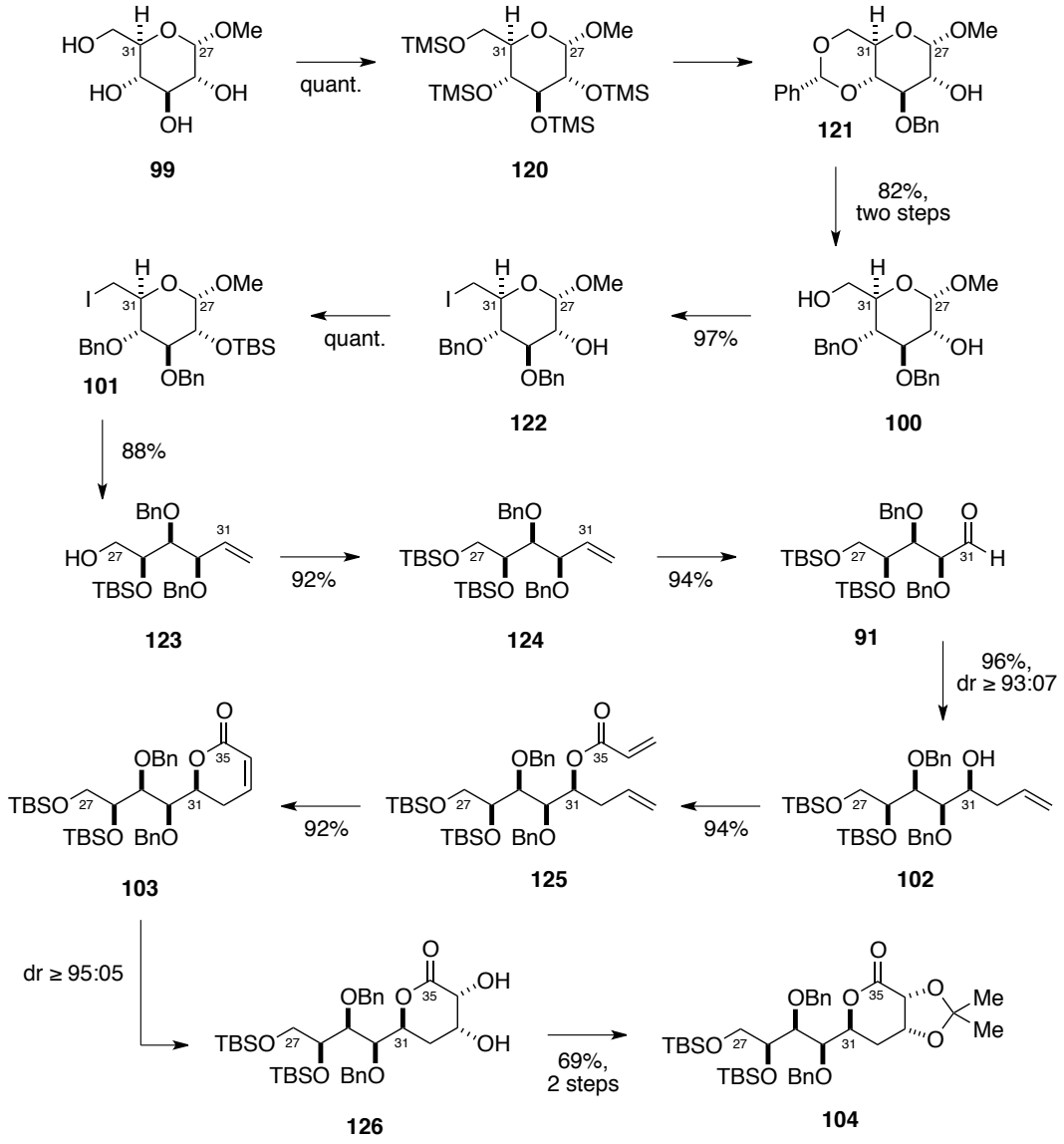


Reagents and conditions: (a) $MgBr_2 \bullet OEt_2$, PMP, CH_2Cl_2, –5 °C, 60%, dr = 95:05; (b) Et_2BOMe, $NaBH_4$, THF, MeOH, –78 °C to –55 °C; aq H_2O_2, pH 7 buffer, MeOH, 0 °C to rt; pinacol, MeOH, 50 °C, 68%, dr = 95:05; (c) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt; (d) H_2, Pd black, dioxane, H_2O, rt, 35% (2 steps).

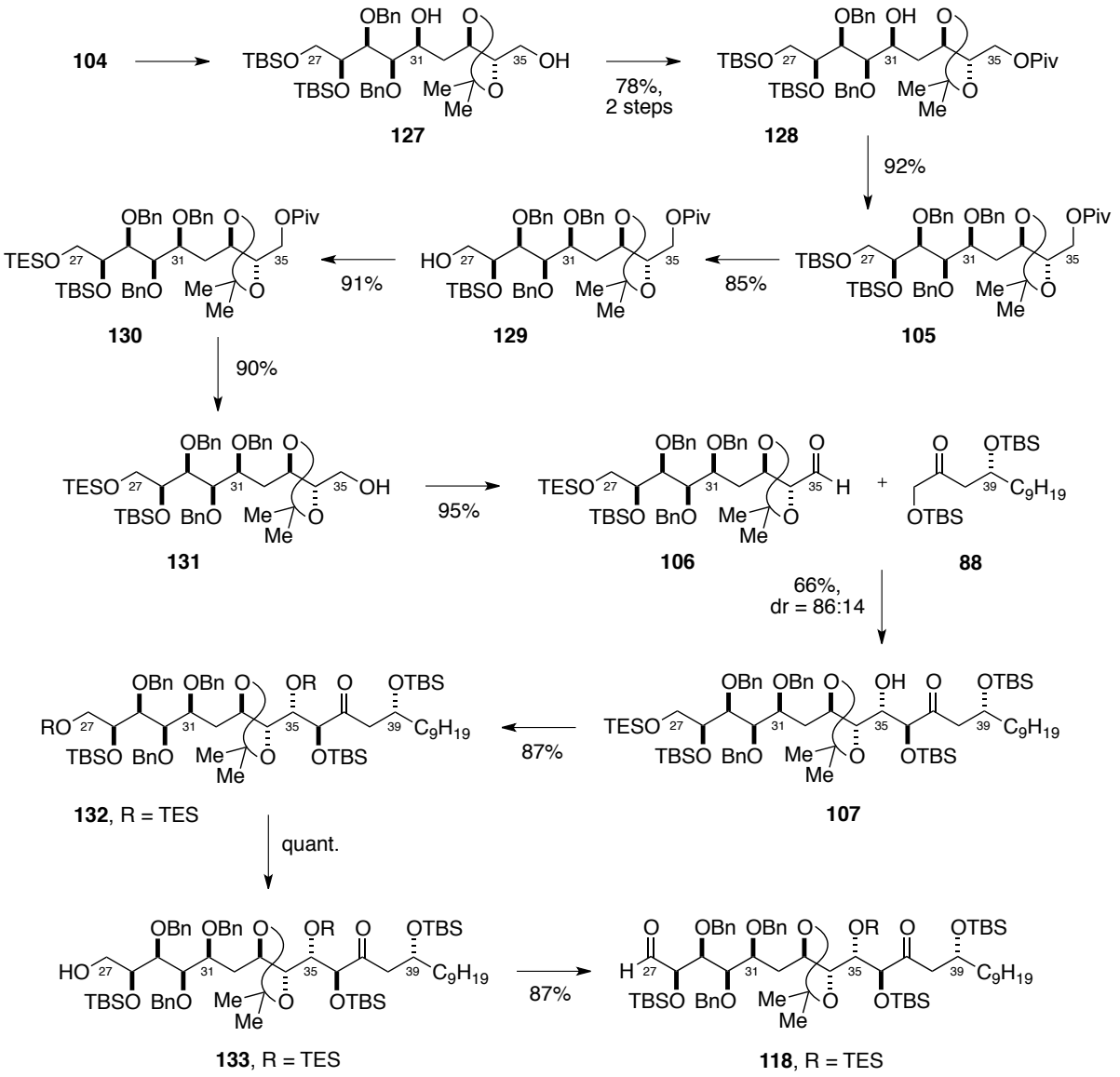
Careful comparison of our NMR spectroscopic data for C3–C48 degradation fragment **20** to that reported by the isolation group for the naturally derived degradation product revealed a structural misassignment.[20] To our surprise, the chemical shifts of the reassigned stereocenters (C8, C9, C28–C31) were in reasonable agreement with our data, but significant differences were observed in the C33–C39 lactol (hemiketal) region. The solution to this structural curiosity and our structural reassignment of naturally derived degradation product **20** will be discussed in Chapter 3.

VI. Graphical Summary

Synthesis of C27–C31 Lactone 104



Synthesis of C27–C48 Aldehyde 118



Chapter

3

Structural Revision of the C3–C48 Degradation Fragment of Aflastatin A

I. Development of a Model for the C27–C48 Lactol Region[1]

We anticipated that synthesis of C3–C48 degradation fragment **1** and comparison of its NMR spectroscopic data to that reported by the isolation group[2] would corroborate the stereochemical revision of aflastatin A (AsA).[2b,3] Despite favorable agreement between our data[4] and the chemical shifts of the reassigned stereocenters in the C8–C9 diol and C27–C31 pentaol regions, we became disappointed when significant differences appeared in the region loosely bound by C33 and C39 (Figure 3.1).

Our analysis revealed a structural misassignment in the lactol region of naturally derived degradation fragment **1**.[4] Since the isolation group reported mass spectrometry data for this molecule,[2a] we believed the correct structure to be an isomer of $C_{53}H_{106}O_{22}$. We could

(1) A model for the C27–C48 lactol region was developed by Dr. Egmont Kattnig in collaboration with Dr. Peter H. Fuller and the author.

(2) (a) Ikeda, H.; Matsumori, N.; Ono, M.; Suzuki, A.; Isogai, A.; Nagasawa, H.; Sakuda, S. *J. Org. Chem.* **2000**, *65*, 438–444; (b) Sakuda, S.; Matsumori, N.; Furihata, K.; Nagasawa, H. *Tetrahedron Lett.* **2007**, *48*, 2527–2531.

(3) Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379–14393.

(4) Kattnig, E. *An Aldol Approach Toward Aflastatin A – Synthesis of the C3–C48 Polyol*. Postdoctoral Report, Harvard University, **2011**.

not rule out the possibility of constitutional isomerism, but the body of two-dimensional NMR, degradation and isotopic labeling experiments conducted by Sakuda and coworkers[2,5] strongly suggested that the structural problem was stereochemical in origin.

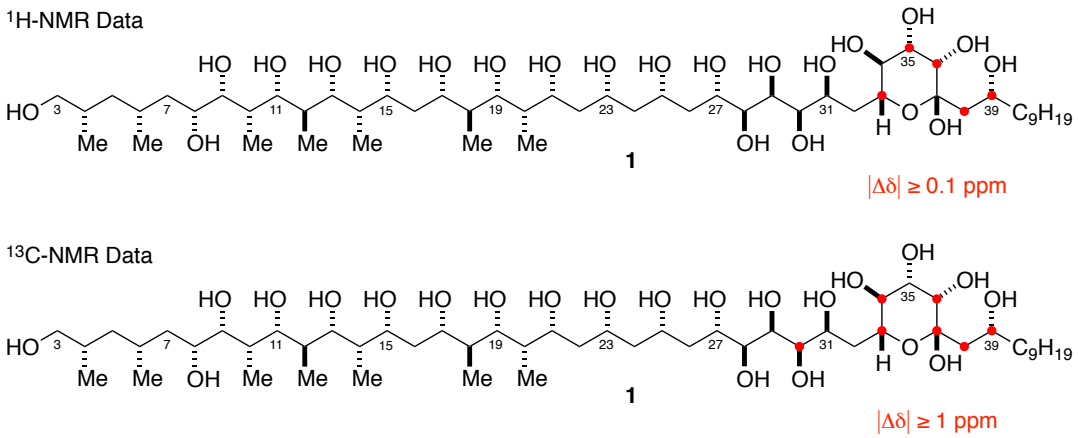


Figure 3.1. NMR data comparisons of synthetic to naturally derived degradation fragment **1**.

We further analyzed the available data to better confine the suspected stereochemical misassignment to the C33–C39 region. At first we used Kishi's NMR database of 1,3,5,7-tetraols[6] to deduce the absolute configuration of the C27 stereocenter (Table 3.1).[4] To begin, the absolute configurations of the C23 and C25 stereocenters had previously been established by Mosher ester and [^{13}C]acetonide analyses,[5c] as well as the independent chemical syntheses of the AsA C9–C27 degradation fragment and its derivatives.[7] We anticipated that the chemical shifts of the C23 and C25 carbon atoms would largely depend upon 1,3-stereochemical relationships within the C21–C27 tetraol region, and be negligibly influenced by the surrounding polypropionate and pentaol regions. Comparison of the corresponding

(5) (a) Sakuda, S.; Ono, M.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Am. Chem. Soc.* **1996**, *118*, 7855–7856; (b) Ono, M.; Sakuda, S.; Ikeda, H.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Antibiotics* **1998**, *51*, 1019–1028; (c) Sakuda, S.; Ikeda, H.; Nakamura, T.; Nagasawa, H. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 407–412.

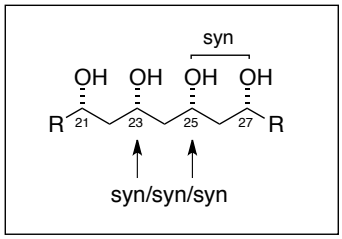
(6) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562–2571.

(7) (a) Evans, D.A.; Trenkle, W.C.; Zhang, J.; Burch, J.D. *Org. Lett.* **2005**, *7*, 3335–3338; (b) Robles, O.; McDonald, F.E. *Org. Lett.* **2008**, *10*, 1811–1814.

values for AsA to Kishi's tetraols revealed a syn/syn/syn stereoarray. Additionally, the chemical shifts of C23 and C25 for the naturally derived[2] and synthetic[4] C3–C48 degradation fragments (**1**) were all within 0.6 ppm of each other, suggesting like syn/syn relationships about each carbon. If a syn/syn/anti stereochemical relationship existed in this region, we expected that the chemical shift of C25 would be approximately 69 ppm, or roughly 2 ppm lesser than C23.[8] Since the absolute configurations of the C23 and C25 stereocenters were known, and the relative 1,3-syn relationship between C25 and C27 duly established, our analysis supported Sakuda's assignment for the C27 stereocenter.

Table 3.1. Chemical shift analysis of the C21–C27 1,3,5,7-tetraol region.[a]

Carbon	Kishi Tetraol (*syn/syn/syn*)[b]	Sakuda Aflastatin A[b]	Sakuda 1 2000[c]	Sakuda 1 2007 Correction[c]	Evans 1[c]
C21	–	73.5	76.2	–	76.3
C23	~68	67.9	70.8	–	70.7
C25	~68	67.5	73.1[d]	71.1	71.3
C27	–	67.9	76.2[e]	72.2	72.3
C28	–	74.3	72.2[e]	76.2	76.1



[a] All chemical shifts (δ) are reported in ppm. [b] Measured in DMSO-d_6. [c] Measured in pyridine-d_5. [d] Value misreported. [e] Values misassigned.

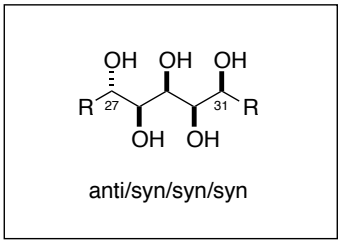
We then compared the spectroscopic profiles of the C27–C31 pentaol regions of naturally derived[2] and synthetic[4] C3–C48 degradation fragments **1** (Table 3.2). Their vicinal proton-proton spin-coupling profiles were similar and suggested that the relative stereochemistry in this region be assigned as anti/syn/syn/syn, according to Kishi's NMR database of 1,2,3,4,5-pentaols.[3] We did note that the C30 carbon atoms differed in chemical shift by 1.2 ppm, but suspected that such disagreement was an artifact of some stereochemical

(8) We assumed that our distribution of chemical shifts in pyridine-d_5 would be similar to those observed by Kishi and coworkers in DMSO-d_6 and methanol-d_4. We did not expect intramolecular interactions (i.e. hydrogen-bonding networks) to significantly impact our analysis.

anomaly in the C33–C39 region.[9] In the end, we trusted the coupling constant analysis and relayed the absolute stereochemistry of the C27 carbinol through the C27–C31 pentaol region, thereby supporting Sakuda's stereochemical revision of the C28–C31 stereocenters.

Table 3.2. Data analysis of the C27–C31 pentaol region.[a]

Coupling Constant Analysis[a]			*Chemical Shift Analysis*[b]		
Protons	**Sakuda 1**[c]	**Evans 1**[c]	**Carbon**	**Sakuda 1**[c]	**Evans 1**[c]
H27–H28	7.5	7.0	C27	72.2[d]	72.3
H28–H29	3.0	2.5	C28	76.2[d]	76.1
H29–H30	5.0	5.5	C29	71.5	71.4
H30–H31	3.0	2.5	C30	75.4	74.2
			C31	70.9	71.0



[a] All coupling constants ($^3J_{H,H}$) are reported in Hertz (Hz). [b] All chemical shifts (δ) are reported in ppm. [c] Measured in pyridine-d_5. [d] Values reassigned in 2007.

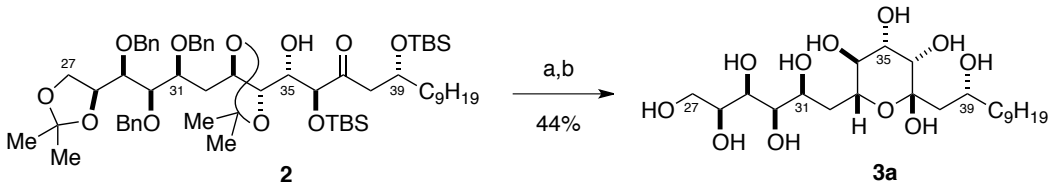
The preceding analyses (Tables 3.1 and 3.2) allowed us to relay the absolute configurations of C23 and C25 to C27 and eventually the entire C27–C31 pentaol region. As such, we limited the potential stereochemical problem to the C33–C39 region wherein the largest contiguous spectral discrepancies existed.

We next developed a model for the C33–C39 region to help us solve the structural curiosity.[4] The model needed to be large enough so that the site of truncation would not affect the chemical shifts of the stereocenters in question. The NMR databases demonstrated that interactions between structural motifs connected directly (α) or with one bridging carbon (β) were significant.[6] Although the influence of structural motifs located outside this "self-contained box" was often negligible, the effects of the γ- and δ-positions on chemical shift profiles were recognizable in some cases.[3] When applied to the C33–C39 region, we identified a self-contained box spanning from C29 to C43. Fortunately, our model studies did

(9) Medium coupling constant values ($^3J_{H,H}$ and $^2J_{C,H}$) were observed by Sakuda and coworkers about the C29–C30 bond. Due to uncertainty in their *J*-based configuration analysis and our C30 chemical shift comparison, we could not fully exclude the possibility of an anti/syn/anti/syn relationship in this region.

not require consumption of advanced intermediate C3–C26 ketone. Rather, we quickly accessed C27–C48 lactol region model **3a** from an intermediate used in the synthesis of C3–C48 degradation fragment **1** (Scheme 3.1).

Scheme 3.1. Synthesis of model C27–C48 lactol **3a**.



Reagents and conditions: (a) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt; (b) H_2, Pd black, dioxane, H_2O, rt, 44% (2 steps).

As hoped, the chemical shifts for model lactol **3a** and synthetic C3–C48 degradation fragment **1** were in good agreement, except at those positions (C27–C29) closest to the site of truncation (Figure 3.2).[4] It followed that similar discrepancies in spectral data for the C33–C39 region were seen between naturally derived[2] C3–C48 degradation **1** and the truncated C27–C48 polyol **3a**.

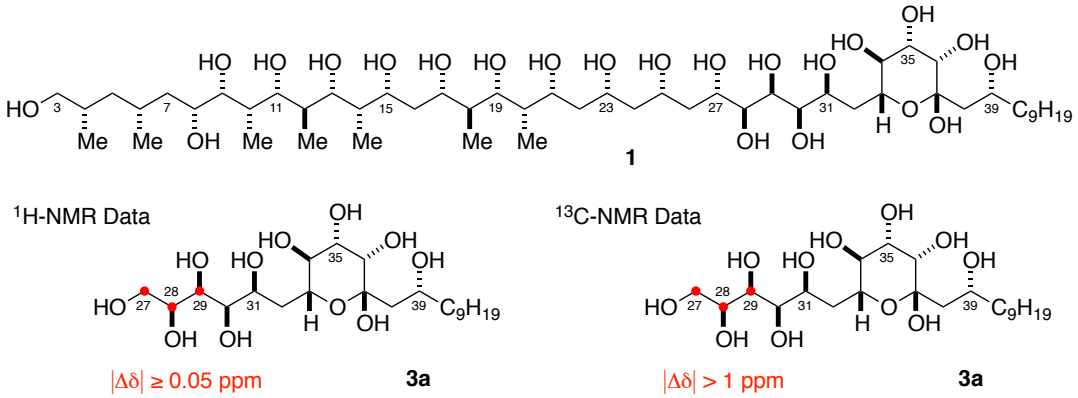


Figure 3.2. NMR data comparisons of model C27–C48 lactol **3a** to synthetic C3–C48 degradation fragment **1**.

As such, we determined that diastereomers of truncated polyol **3a** could serve as suitable models of the lactol region in our future studies toward the stereochemical revision of AsA. Ideally, once a spectral match was obtained, we could parlay our work on that model diastereomer into the synthesis of a revised C27–C48 aldehyde fragment.

II. Syntheses of the epi-C39 and epi-C33–C37 Lactols

We revisited the chemical shift discrepancies between synthetic[4] and naturally derived[2] degradation fragments **1** and were intrigued that the largest numerical differences occurred from C36–C39 in the carbon spectra, and at H33, H38 and H39 in the proton spectra. These observations prompted us to question the stereochemical relationships between the C27–C31 pentaol region and the C33–C37 lactol, as well as the C33–C37 lactol and the isolated C39 stereocenter.

The absolute configurations at C39 and C33 of AsA were determined by optical rotation analyses of small degradation fragments **4**[10] and **5**, respectively (Figure 3.3).[2a] We noticed that the *J*-based configuration analysis[11] used to link the absolute configurations of C31 and C33 before the stereochemical revision of AsA was later discarded.[2b] With this in mind, we decided to check the validity of the optical rotation data through chemical syntheses of epi-C39 and epi-C33–C37 lactol regions **3b** and **3c**, respectively. The latter diastereomer was designed to be epimeric at C33 and by necessity throughout the entire C33–C37 region in order to preserve the relative stereochemistry within the lactol ring, as supported by published coupling constant and NOE data.[5a,b]

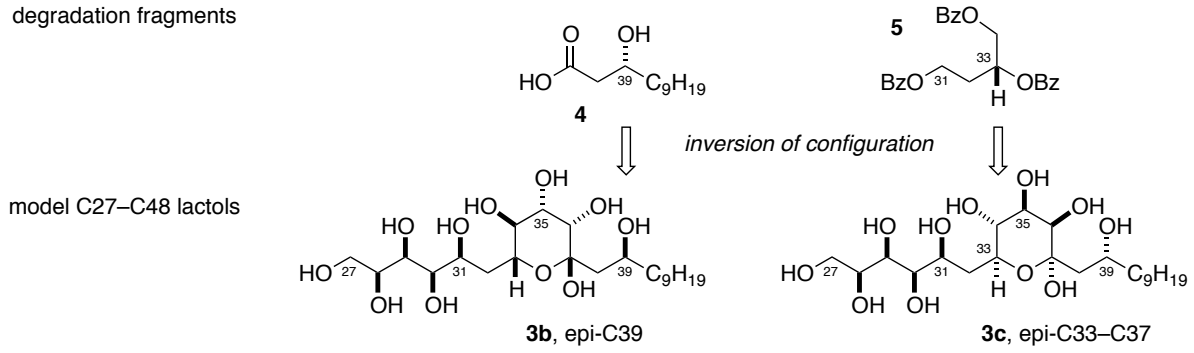


Figure 3.3. Design of model C27–C48 lactols **3b** and **3c** to probe optical rotation data.

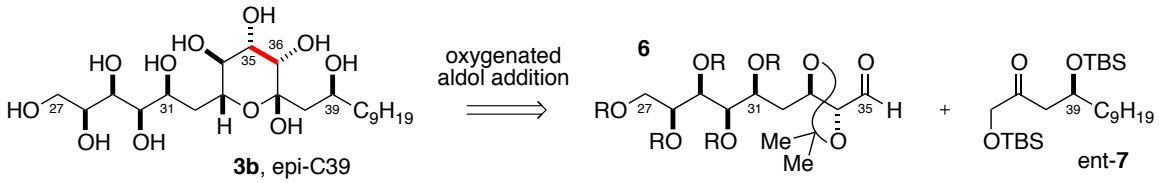
(10) Vining, L.C.; Taber, W.A. *Can. J. Chem.* **1962**, *40*, 1579–1584.

(11) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866–876.

A. Synthesis of the epi-C39 Lactol[12]

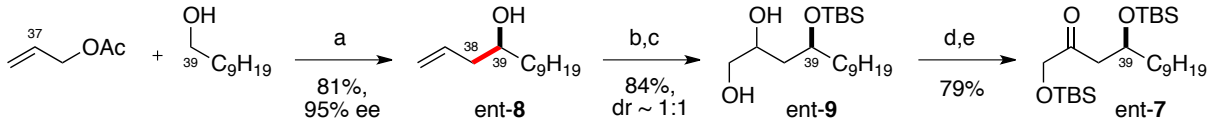
The first truncated polyol that we targeted was the C39 epimer (**3b**). Our synthesis plan for this diastereomer targeted the same C35–C36 aldol bond disconnection,[13] except that enantiomeric ketone ent-**7** would be added to common aldehyde intermediate **6** (Scheme 3.2).

Scheme 3.2. Synthesis plan for epi-C39 lactol **3b**.



We took this opportunity to further improve the synthesis of the C36–C48 ketone (Scheme 3.3).[14] Our route featured the iridium-catalyzed transfer hydrogenative allylation[15] of 1-decanol to give homoallylic carbinol ent-**8** in very good yield and excellent enantioselection. Silylation and dihydroxylation[16] afforded diol ent-**9**. Regioselective silylation and Parikh-Doering oxidation[17] then gave α-silyloxyketone ent-**7** in five steps and good overall yield.

Scheme 3.3. Synthesis of C36–C48 ketone ent-**7**.



Reagents and conditions: (a) $[Ir(cod)Cl]_2$ (2.5 mol%), (*R*)-(+)-BINAP, Cs_2CO_3, *m*-NO_2BzOH, THF, 100 °C, 81%, 95% ee; (b) TBSCl, imidazole, DMF, 0 °C to rt; (c) $RuCl_3$, $CeCl_3•7H_2O$, $NaIO_4$, EtOAc, MeCN, H_2O, 0 °C, dr ~ 1:1, 84% (2 steps); (d) TBSCl, imidazole, DMF, 0 °C to rt, 93%; (e) $SO_3•Py$, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –10 °C to 10 °C, 85%.

---

(12) The synthesis of epi-C39 lactol **3b** was achieved by the author in collaboration with Drs. Egmont Kattnig and Peter H. Fuller.

(13) (a) Glorius, F. *Development of α-Oxygenated Aldol Methodology and Progress Towards the Synthesis of Aflastatin A*. Postdoctoral Report, Harvard University, **2001**; (b) Evans, D.A.; Glorius, F.; Burch, J.D. *Org. Lett*. **2005**, *7*, 3331–3335.

(14) This reaction sequence was designed and performed by Dr. Peter H. Fuller.

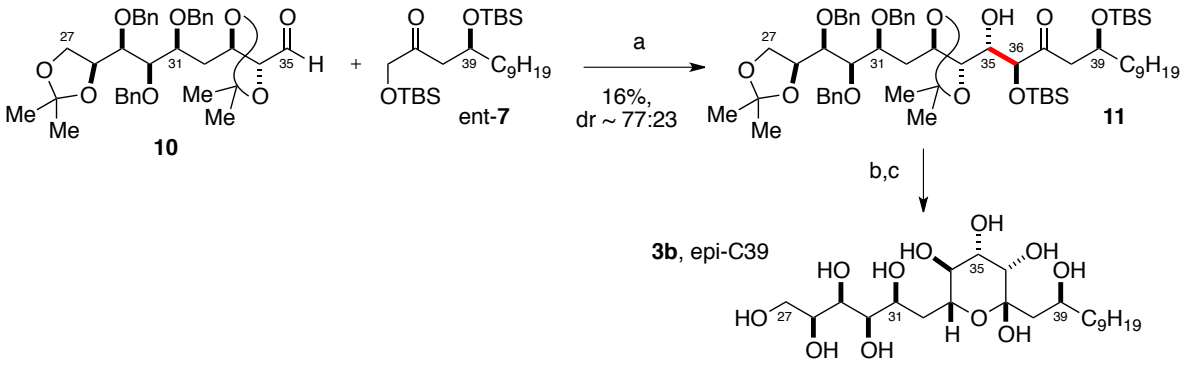
(15) Kim, I.S.; Ngai, M.-Y.; Krische, M.J. *J. Am. Chem. Soc*. **2008**, *130*, 14891–14899.

(16) (a) Plietker, B.; Niggemann, M. *J. Org. Chem*. **2005**, *70*, 2402–2405; (b) Plietker, B. *Synthesis* **2005**, 2453–2472.

(17) Parikh, J.R.; Doering, W.v.E. *J. Am. Chem. Soc*. **1967**, *89*, 5505–5507.

With C27–C35 aldehyde **10** in hand,[4] the synthesis of epi-C39 lactol **3b** was three steps from completion (Scheme 3.4). Addition of the corresponding (*E*) enolate of ketone ent-**7** to aldehyde **10** produced the desired anti-Felkin product **11** in poor isolated yield[18] but with a similar level of diastereoselection previously observed en route to lactol **3a** (dr = 84:16). The inverted stereochemistry (C39) at the β'-position of ketone ent-**7** had a minimal impact on C35–C36 aldol reaction diastereoselectivity. Ultimately, removal of the acetonide, silyl and benzyl protecting groups provided epi-C39 lactol **3b** in serviceable yield.

Scheme 3.4. Synthesis of epi-C39 lactol **3b**.



Reagents and conditions: (a) ketone *ent*-**7**, Cy_2BCl, Me_2NEt, pentane, 0 °C to rt; aldehyde **10**, PhMe, –78 °C to –25 °C, 16%, dr ~ 77:23; (b) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt, 50%; (b) H_2, Pd black, dioxane, H_2O, rt.

B. Synthesis of the epi-C33–C37 Lactol[19]

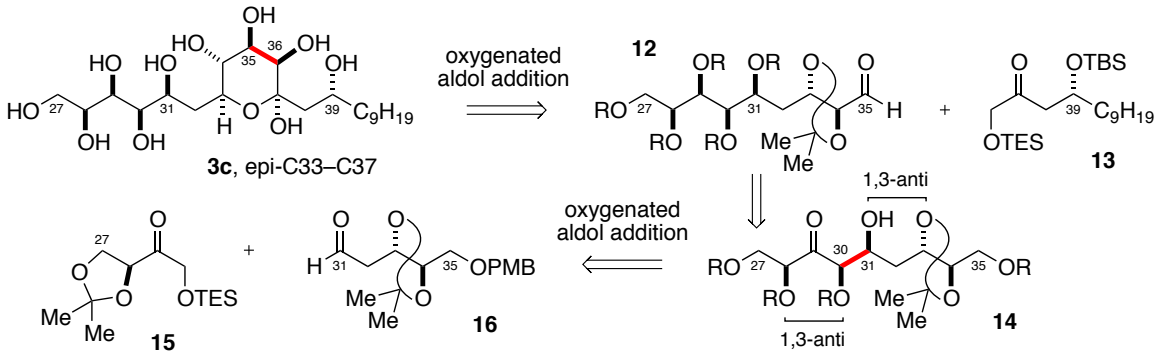
The second truncated polyol that we targeted was the C33–C37 epimer (**3c**). Our synthesis plan for this diastereomer again targeted the C35–C36 aldol bond disconnection[13] because inversion of the entire lactol preserved the anti/syn/anti relationship required for this transform (Scheme 3.5). Additionally, we expected the diastereoselectivity of this reaction to be restored to the excellent levels seen before the revision since the relative configuration

(18) The quality of the chlorodicyclohexylborane used in this reaction was questionable. For the best results, we distilled Cy_2BCl at least once every 3 months and stored it under argon in a Schlenck flask at –20 °C.

(19) The synthesis of epi-C33–C37 lactol **3c** was achieved by the author in collaboration with Drs. Egmont Kattnig and Peter H. Fuller.

between the C31 and C33 carbinol stereocenters was again 1,3-anti.[13b,20] The C27–C35 fragment **14** would in turn be assembled via the double stereodifferentiating syn aldol addition of α,α'-bisoxygenated ketone **15**[21] to β-oxygenated aldehyde **16**. We expected excellent diastereoselection due to the matched relationship between the ketone α'-stereocenter and the aldehyde β-stereocenter. Dipole-dipole minimization within both ketone[22] and aldehyde[23] would determine their respective facial selectivities, and bond formation would occur on each reactant's less sterically hindered face.

Scheme 3.5. Synthesis plan for epi-C33–C37 lactol **3c**.



We took this opportunity to modify the protecting group scheme of the C36–C48 ketone. We finally decided to protect the C36 carbinol as its TES ether[24] rather than its TBS ether because removal of the latter protecting group during our previous fragment and model

(20) (a) Zhang, J. *Studies Toward the Total Synthesis of (–)-Aflastatin A*. Postdoctoral Report, Harvard University, **2003**; (b) Burch, J.D. *Complex Aldol Reactions for Polyketide Synthesis: I. Total Synthesis of Callipeltoside A. II. Synthesis of the C27–C48 Subunit of Aflastatin A*. Ph.D. Thesis, Harvard University, **2005**.

(21) Chlorodicyclohexylboron-mediated aldol reactions of α-triethylsilyloxyketone **15** were known to produce *syn* products via the corresponding (*Z*) enolate. See: (a) Marco, J.A.; Carda, M.; Falomir, E.; Palomo, C.; Oiarbide, M.; Ortiz, J.A.; Linden, A. *Tetrahedron Lett*. **1999**, *40*, 1065–1068; (b) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J.A. *Tetrahedron* **2000**, *56*, 677–683; (c) Ribes, C.; Falomir, E.; Carda, M.; Marco, J.A. *Org. Lett*. **2007**, *9*, 77–80.

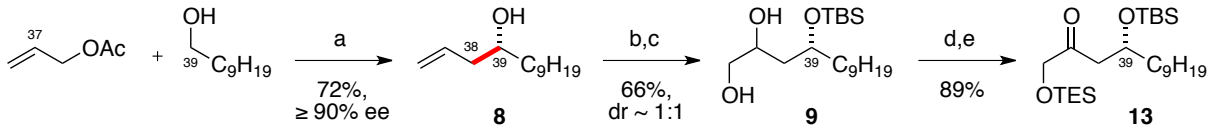
(22) (a) Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. *J. Am. Chem. Soc*. **1981**, *103*, 1566–1568; (b) Heathcock, C.H.; Arseniyadis, S. *Tetrahedron Lett*. **1985**, *26*, 6009–6012; (c) Bernardi, A.; Capelli, A.M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J.M. Paterson, I. *Tetrahedron* **1991**, *47*, 3471–3484.

(23) Evans, D.A.; Dart, M.J.; Duffy, J.L.; Yang, M.G. *J. Am. Chem. Soc*. **1996**, *118*, 4322–4343.

(24) Boron-mediated aldol reactions of α-triethylsilyloxyketones were known. For examples, see: Ref. 21.

syntheses was difficult.[4] The synthesis of C36–C48 ketone **13** (Scheme 3.6) was achieved in similar fashion to its pseudo-enantiomer ent-**7** (Scheme 3.3). As a point of difference, regioselective triethylsilylation of diol **9** and oxidation[17] of the intermediate C37 carbinol gave C36–C48 ketone **13** in five steps and good overall yield.

Scheme 3.6. Synthesis of C36–C48 ketone **13**.



Reagents and conditions: (a) $[Ir(cod)Cl]_2$ (2.5 mol%), (*S*)-(+)-BINAP, Cs_2CO_3, *m*-NO_2BzOH, THF, 100 °C, 72%, ≥ 90% ee; (b) TBSCl, imidazole, DMF, 0 °C to rt, 90%; (c) $RuCl_3$, $CeCl_3$•$7H_2O$, $NaIO_4$, EtOAc, MeCN, H_2O, 0 °C, dr ~ 1:1, 73%; (d) TESCl, $EtN(iPr)_2$, CH_2Cl_2, –60 °C to –20 °C, 90%; (e) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C, 99%.

The synthesis of epi-C33–C37 lactol **3c** began with the preparation of ketone **15** in six steps from L-ascorbic acid,[25] and aldehyde **16** in five steps from (–)-2,3-*O*-isopropylidene-D-erythronolactone[26] (Scheme 3.7). Addition of the (*Z*) boron enolate derived from ketone **15** to aldehyde **16** provided adduct in good yield with excellent diastereoselection.[27] Prasad reduction,[28,29] protecting group manipulation, and oxidation[17] provided aldehyde **19** in good overall yield. As expected, anti aldol addition of ketone **13** to this aldehyde provided adduct **20** as a single diastereomer in good overall yield. Ultimately, the now standard two-step deprotection sequence yielded epi-C33–C37 lactol **3c**.

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(25) Marco, J.A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J. *Liebigs Ann. Chem.* **1996**, 1801–1810.

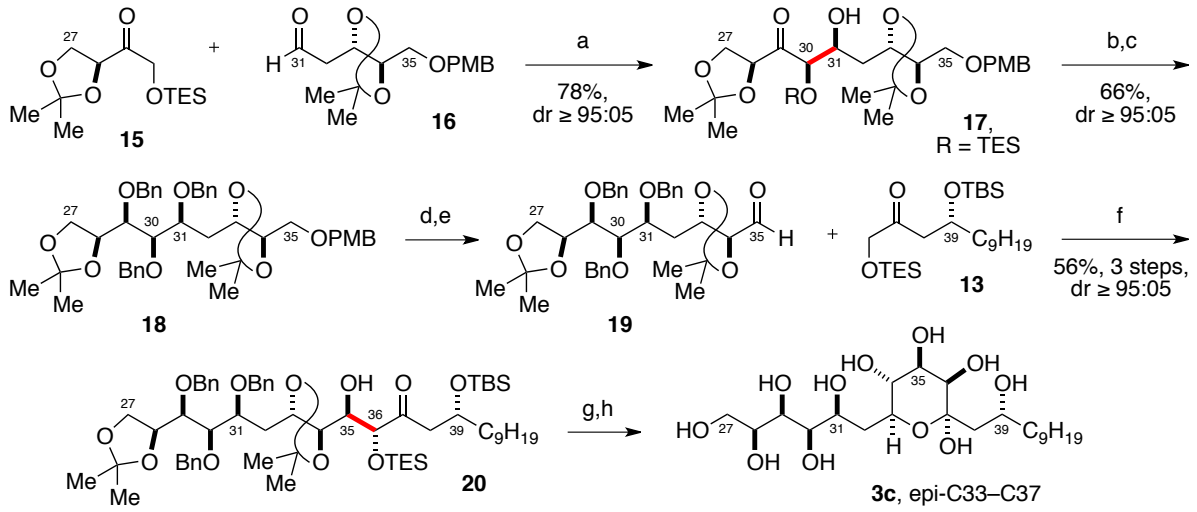
(26) For steps related to the synthesis of aldehyde **16**, see: (a) Choi, W.J.; Park, J.G.; Yoo, S.J.; Kim, H.O.; Moon, H.R.; Chun, M.W.; Jung, Y.H.; Jeong, L.S. *J. Org. Chem.* **2001**, *66*, 6490–6494; (b) Pirrung, F.O.H.; Hiemstra, H.; Speckamp, W.N.; Kaptein, B.; Schoemaker, H.E. *Synthesis* **1995**, 458–472; (c) Brown, H.C.; Mandal, A.K.; Kulkarni, S.U. *J. Org. Chem.* **1977**, *42*, 1392–1398; (d) Kang, S.-K.; Jung, K.-Y.; Chung, J.-U.; Namkoong, E.-Y.; Kim, T.-H. *J. Org. Chem.* **1995**, *60*, 4678–4679.

(27) The stereochemistry of the newly formed stereogenic center was determined by Mosher ester analysis. See: (a) Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519; (b) Hoye, T.R.; Jeffrey, C.S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451–2458.

(28) Chen, K.-M.; Hardtmann, G.E.; Prasad, K.; Repič, O; Shapiro, M.J. *Tetrahedron Lett.* **1987**, *28*, 155–158.

(29) The stereochemistry of the newly formed stereogenic center was determined by [^{13}C]acetonide analysis. See: Rychnovsky, S.D.; Rogers, B.N.; Richardson, T.I. *Acc. Chem. Res.* **1998**, *31*, 9–17.

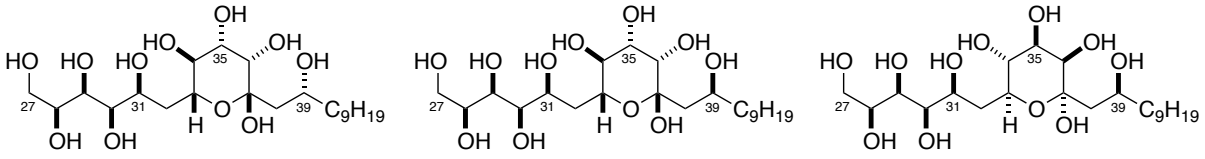
Scheme 3.7. Synthesis of epi-C33–C37 lactol **3c**.



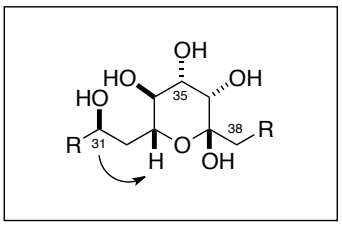
Reagents and conditions: (a) Cy_2BCl, Et_3N, Et_2O, –78 °C to 0 °C, dr ≥ 95:05, 78% (2 steps); (b) Et_2BOMe, $NaBH_4$, THF, MeOH, –78 °C to 0 °C; aq H_2O_2, pH 7 buffer, MeOH, 0 °C to rt, 92%, dr ≥ 95:05; (c) CsF, THF, 70 °C; BnBr, NaH, nBu_4NI, 0 °C to rt, 72%; (d) DDQ, CH_2Cl_2, pH 7 buffer, 0 °C, no hν, 81%; (e) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C; (f) ketone **13**, Cy_2BCl, Me_2NEt, pentane, 0 °C to rt; aldehyde **19**, Et_2O, –78 °C to –25 °C, dr ≥ 95:05, 56% (3 steps); (g) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt; (h) H_2, Pd black, dioxane, H_2O, rt.

After completing the syntheses of lactols **3b** and **3c**, we once again compared spectroscopic data. Coupling constant analysis ($^3J_{H31–H32}$) revealed that the stereochemical relationship between C31 and the lactol was correct in diastereomers **3a** and **3b**, but not epi-C33–C37 lactol **3c** (Table 3.3). As expected, the degradation fragments and model lactols all exhibited similar spin-coupling profiles around the C33–C37 lactol.

Table 3.3. Coupling constant analysis of the C31–C36 region.[a]



Protons	Sakuda 1	Synthetic 1[b]	Lactol 3a[c]	Lactol 3b[c]	Lactol 3c[c]
H31–H32	6.0, 8.0[b]	6.6, 7.8	6.3, 7.6	5.5, 7.3	2.9, 10.0
H32–H33	3.5, 10.0[b]	3.0, 10.2	2.9, 10.2	2.7, 9.5	2.9, 10.0
H33–H34	9.5[d]	9.6	9.7	9.5	9.7
H34–H35	9.5[d]	9.6	9.5	9.5	9.5
H35–H36	3.0[d]	3.0	3.4	3.4	3.4

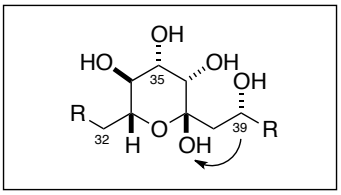


[a] All coupling constants ($^3J_{H,H}$) are reported in Hertz (Hz). [b] Measured in pyridine-d_5. [c] Measured in methanol-d_4. [d] Measured in DMSO-d_6.

Chemical shift analysis in the C38–C39 region was not as conclusive (Table 3.4). We were hard pressed to explain the relative positional flip of the H38 protons throughout the series. Ultimately, we surmised that the absolute configurations at both C33 and C39 were assigned properly.[30]

Table 3.4. Chemical shift analysis of the C38–C39 region.

Protons	Sakuda 1[b]	Synthetic 1[b]	Lactol 3a[b]	Lactol 3b[b]	Lactol 3c[b]
H38a[c]	2.45	2.14	2.16	2.48	2.38
H38b[d]	2.19	2.73	2.74	2.62	2.70
H39	4.18	4.72	4.73	4.59	4.56



[a] All chemical shifts (δ) are reported in ppm. [b] Measured in pyridine-d_5. [c] Observed peak a doublet of doublets having two large coupling constants. [d] Observed peak a doublet of doublets having one large and one small coupling constant.

III. Syntheses of Three Diastereomeric epi-C36 Lactols

Having substantiated the stereochemical assignments at C33 and C39 with our own data, we refocused on the remaining structural ambiguities in the lactol region. We reasoned that due to conformational and anomeric effects, the configuration at C33 should control C37, thus leaving three stereocenters (C34–C36) in question (Figure 3.4A). Now limited to eight possible diastereomers, we scrutinized the published spectra for further guidance. Out of all the peaks associated with the C34–C36 triol, one distinct doublet of doublets (dd) was identified in the ^{1}H-NMR spectrum (Figure 3.4B).[2a] Assuming a chair conformation, the requirement that a proton within the lactol ring exhibit one large (L) and one small (S) coupling constant (or be anti and gauche to vicinal protons, respectively) reduced the field to four diastereomers (Figure 3.4C), one of which was the originally assigned structure (**3a**). Our highest priority became the synthesis of a structure (**3d**) that agreed with the proposed

(30) The corresponding C31 and C37 stereocenters of blasticidin A were assigned the same absolute configuration. See: (a) Sakuda, S.; Ono, M.; Ikeda, H.; Inagaki, Y.; Nakayama, J.; Suzuki, A.; Isogai, A. *Tetrahedron Lett*. **1997**, *38*, 7399–7402; (b) Sakuda, S.; Ono, M.; Ikeda, H.; Nakamura, T.; Inagaki, Y.; Kawachi, R.; Nakayama, J.; Suzuki, A.; Isogai, A.; Nagasawa, H. *J. Antibiotics* **2000**, *53*, 1265–1271.

assignment of this peak to H35 (Figure 3.4D). Should we suspect that the two-dimensional NMR correlation data had been misinterpreted and the peak actually corresponds to H34, both structures **3e** and **3g** would become viable synthesis candidates. We were open to this possibility because a similar error may have led to the correction (and formal swap) of chemical shift data sets for C27 and C28 when the stereochemical revision was reported.[2b]

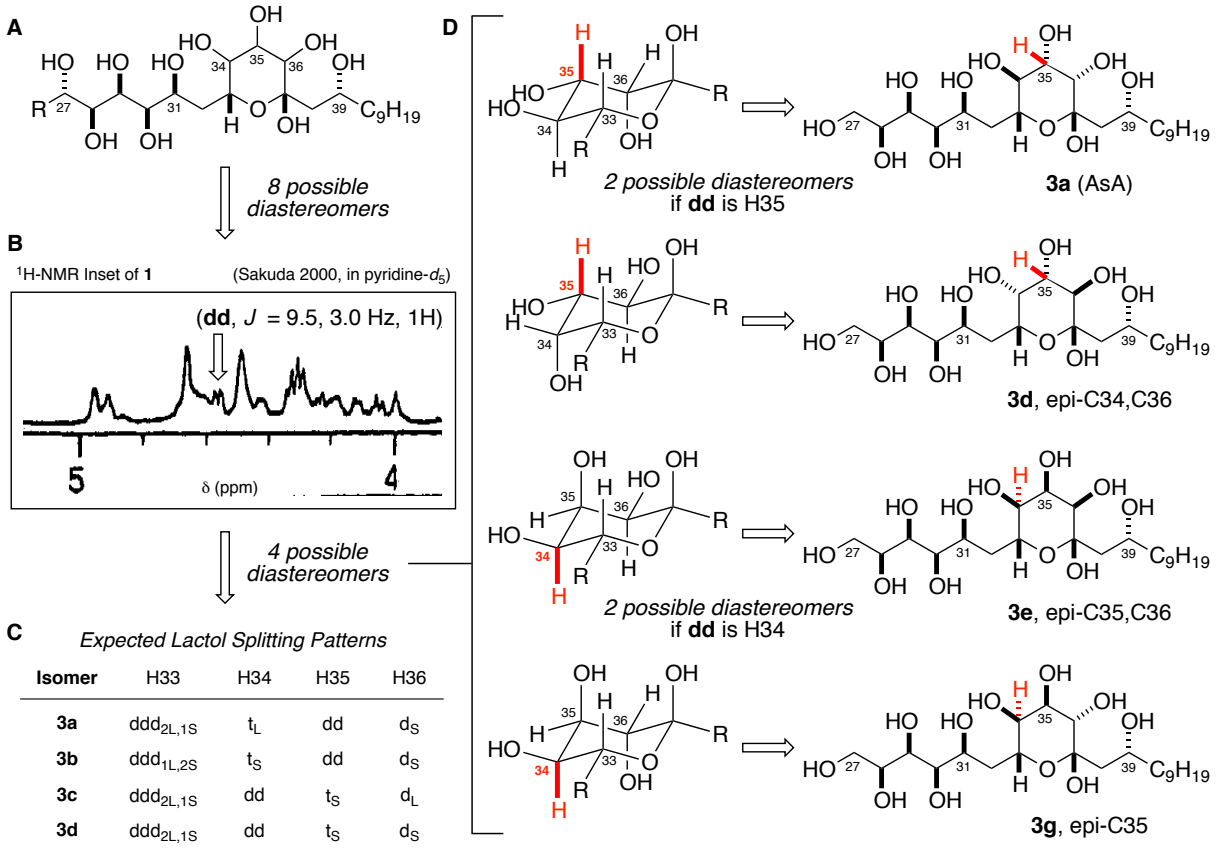


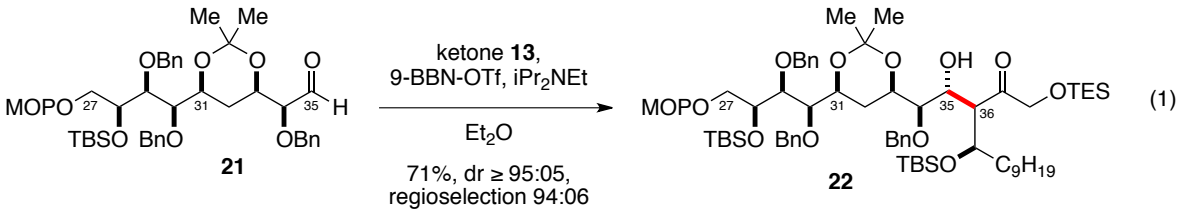
Figure 3.4. Design of model C27–C48 lactols **3d**, **3e** and **3g** to probe two-dimensional NMR correlation data. Abbreviations: d = doublet, t = triplet, S = having a small *J* value(s), L = having a large *J* value(s).

A. Synthesis of the epi-C34,C36 Lactol[31]

Under this rationale, we first targeted the synthesis of epi-C34,C36 lactol **3d**. Since the relative stereochemistry of the C33–C36 tetraol region was changed, we could no longer form

(31) The synthesis of epi-C34,C36 lactol **3d** was achieved by Dr. Peter H. Fuller in collaboration with the author.

the C35–C36 bond by anti-Felkin-selective oxygenated aldol addition.[13] Instead, we tried to form this bond by the Cornforth-selective syn aldol addition[32] of ketone **13** to aldehyde **21**, but these efforts were stymied by an unexpected reversal in enolate regioselectivity[33] (eq 1).



(1)

We then modified our synthesis plan such that the assembly of the C33–C36 *syn/anti/syn* tetraol relied on the diastereoselective syn dihydroxylation[16] of enone **24** according to Kishi's empirical rule[34] (Scheme 3.8). The C35–C36 bond of enone **24** would in turn be formed by the Horner-Wadsworth-Emmons reaction[35] of β-ketophosphonate **26** and aldehyde **25**. Then, given the success of our newly developed chelate-controlled aldol reaction, we anticipated applying our soft-enolization based method[4] to the formation of the C32–C33 bond via 1,2-chelate-controlled addition of ketone **27** to aldehyde **28**. Based upon the Cram chelate model,[36] we expected excellent selectivity for the desired 1,2-syn diastereomer via exclusive formation of five-membered chelate **29** and nucleophilic addition to the less sterically hindered face.

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(32) (a) Cornforth, J.W.; Cornforth, R.H.; Mathew, K.K. *J. Chem. Soc.* **1959**, 112–127; (b) Evans, D.A.; Siska, S.J.; Cee, V.J. *Angew. Chem., Int Ed.* **2003**, *42*, 1761–1765; (c) Cee, V.J. *I. Asymmetric Induction in Heteroatom-Substituted Aldehydes. II. Total Synthesis of (+)-Casuarine*. Ph.D. Thesis, Harvard University, **2003**.

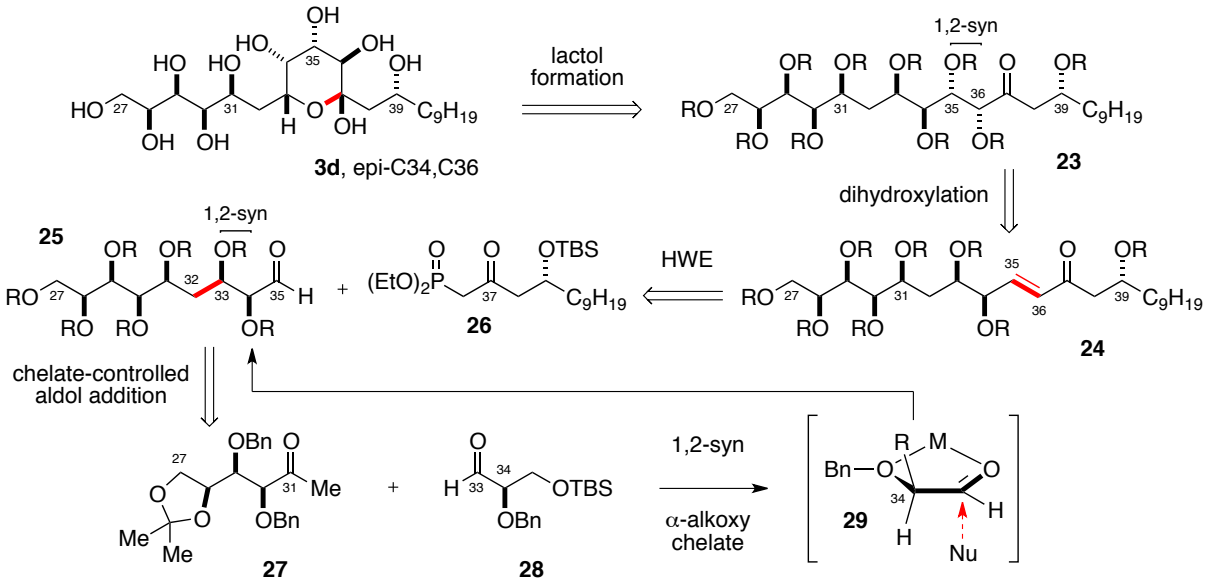
(33) Products resulting from α'-enolization were not observed in earlier chlorodicyclohexylboron-mediated aldol additions of C36–C48 ketones. See: Ref. 13.

(34) (a) Cha, J.K.; Christ, W.J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943–3946; (b) Cha, J.K.; Christ, W.J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247–2255.

(35) (a) Horner, L.; Hoffman, H.; Wippel, H.G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499–2505; (b) Wadsworth, W.S., Jr.; Emmons, W.D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.

(36) (a) Cram, D.J.; Abd Elhafez, F.A. *J. Am. Chem. Soc.* **1952**, *74*, 5828–5835; (b) Cram, D.J.; Kopecky, K.R. *J. Am. Chem. Soc.* **1959**, *81*, 2748–2755; (c) Cram, D.J.; Leitereg, T.H. *J. Am. Chem. Soc.* **1968**, *90*, 4019–4026.

Scheme 3.8. Synthesis plan for epi-C34,C36 lactol **3d**.



The synthesis of lactol **3d** began with the preparation of ketone **27** in eight steps from methyl α-D-(+)-glucopyranoside,[37] aldehyde **28** in six steps from glycidol,[38] and β-ketophosphonate **26** in three steps from diol **9** (Scheme 3.9).[39] 1,2-Chelation-controlled addition of ketone **27** to aldehyde **28** under soft enolization conditions proceeded with excellent diastereoselection. Prasad reduction[28] of the intermediate adduct to diol **30**, acetonide formation, desilylation and oxidation[17] at C35 yielded aldehyde **32**. Barium hydroxide-mediated addition[40] of phosphonate **26** to this aldehyde provided (*E*) enone **33** as a single isomer in good overall yield. As predicted by Kishi's empirical rule,[34] dihydroxylation[16] provided the desired 1,2-syn diol **34** in good yield and diastereoselection. Finally, the standard deprotection sequence gave epi-C34,C36 lactol **3d**.

---

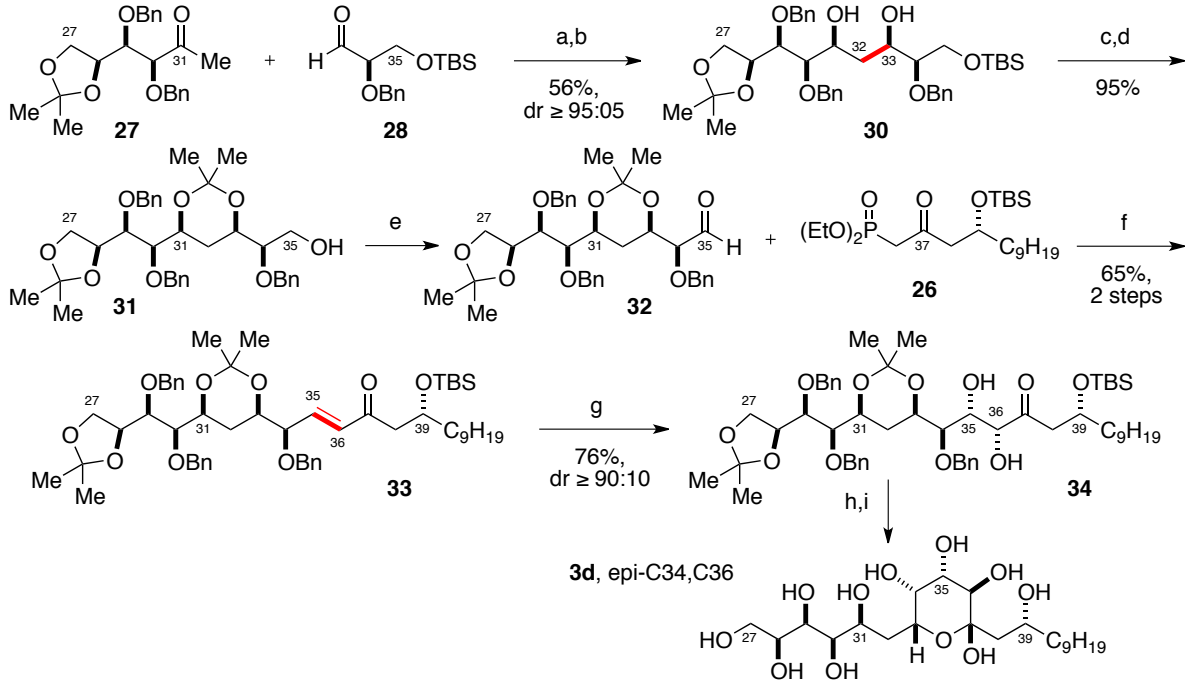
(37) The synthesis of the C27–C31 aldehyde precursor to ketone **27** will be discussed in due course.

(38) (a) Kolakowski, R.V.; Williams, L.J. *Tetrahedron Lett.* **2007**, *48*, 4761–4764; (b) Furrow, M.E.; Schaus, S.E.; Jacobsen, E.N. *J. Org. Chem.* **1998**, *63*, 6776–6777.

(39) For an analogous synthesis of a structurally related β-ketophosphonate, see: Traoré, M.; Maynadier, M.; Souard, F.; Choisnard, L.; Vial, H.; Wong, Y.-S. *J. Org. Chem.* **2011**, *76*, 1409–1417.

(40) (a) Alvarez Ibarra, C.; Arias, S.; Fernández, M.J.; Sinisterra, J.V. *J. Chem. Soc., Perkin Trans. II* **1989**, 503–508; (b) Paterson, I.; Yeung, K.-S.; Smaill, J.B. *Synlett* **1993**, 774–776.

Scheme 3.9. Synthesis of epi-C34,C36 lactol **3d**.



Reagents and conditions: (a) $MgBr_2$•OEt_2, PMP, CH_2Cl_2, –5 °C, dr ≥ 95:05; (b) Et_2BOMe, $NaBH_4$, THF, MeOH, –78 °C to 0 °C; aq H_2O_2, NaOH, MeOH, 0 °C to rt, dr ≥ 95:05, 56% (2 steps); (c) $Me_2C(OMe)_2$, PPTS, acetone, rt, quant.; (d) Et_3N•HF, THF, 0 °C to rt, 95%; (e) SO_3•Py, EtN(iPr)$_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C; (f) $Ba(OH)_2$, THF, H_2O, 0 °C to 10 °C, 65% (2 steps); (g) $RuCl_3$, $CeCl_3$•$7H_2O$, $NaIO_4$, EtOAc, MeCN, H_2O, 0 °C, 76%, dr ≥ 90:10; (h) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt, ~70%; (i) H_2, Pd black, dioxane, H_2O, rt.

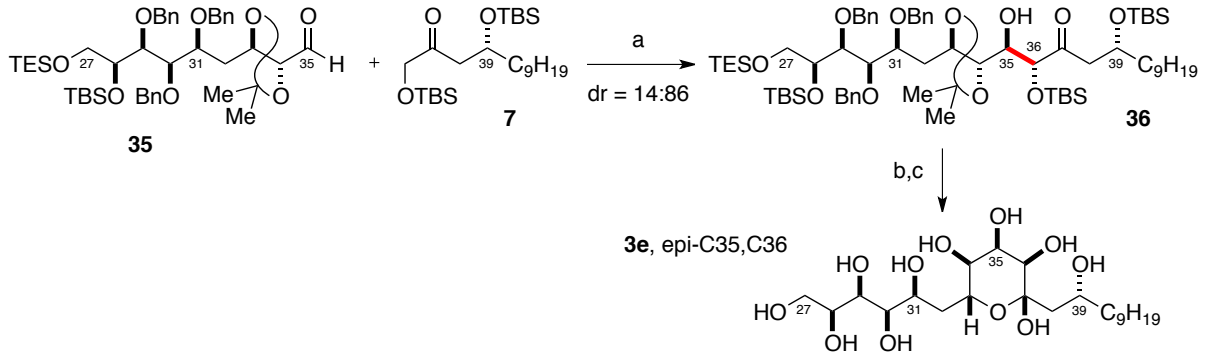
After completing the synthesis of lactol **3d**, we were initially disappointed by how poorly its spectroscopic data matched that of polyol **1**. Upon further analysis, we did observe a favorable exchange of the H38 resonances, most likely resulting from the inverted configuration at C36, and decided this effect deserved further investigation. Accordingly, we prioritized the synthesis of epi-C35,C36 lactol **3e** over that of epi-C35 lactol **3g**.

B. Synthesis of the epi-C35,C36 Lactol[41]

Somewhat serendipitously, a precursor to epi-C35,C36 lactol **3e** had already been isolated as the minor (Felkin) diastereomer in the earlier anti aldol addition of ketone **7** to aldehyde **35** (Scheme 3.10). Two-step global deprotection of this aldol product provided epi-C35,C36 lactol **3e**.

(41) The synthesis of epi-C35,C36 lactol **3e** was achieved by the author in collaboration with Dr. Peter H. Fuller.

Scheme 3.10. Synthesis of epi-C35,C36 lactol **3e**.



Reagents and conditions: (a) ketone **7**, Cy_2BCl, Me_2NEt, pentane, 0 °C to rt; aldehyde **35**, PhMe, –78 °C to –20 °C, 66%, dr = 14:86; (b) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt, 53%; (c) H_2, Pd black, dioxane, H_2O, rt.

Comparison of the spectroscopic data for lactol **3e** with naturally derived[2] degradation polyol **1** produced the best chemical shift match to date for the methylene protons at C32 and C38 while maintaining the same beneficial interchange of H38 resonances that were observed for lactol **3d**. The excellent overlay of these diagnostic peaks suggested that the relative stereochemistries in lactol **3e** between the C34 stereocenter and the C27–C31 pentaol region, and the C36 stereocenter and the isolated C39 stereocenter, were correct. Disappointingly, much of the spectroscopic data within the lactol ring itself still exhibited poor overlay. We hypothesized that this could be rectified by inverting the stereochemistry at C35 to its originally assigned configuration (Figure 3.5). In doing so, we discredited a coupling constant that was assigned to this region ($^3J_{H\text{-}35,H\text{-}36}$ = 3 Hz).[5a] The possibility that a coupling constant had been measured incorrectly was not so unreasonable since the correction of one value ($^3J_{H\text{-}9,H\text{-}10}$) by the isolation group led to the stereochemical revision of the AsA C8–C9 diol region.[2b] Unfortunately, this possibility was also inconsistent with our previous spectral analysis, namely the assumption that a doublet of doublets (having one small *J* value of about 3 Hz) corresponds to either H34 or H35. Out of both desperation and curiosity, we proceeded anyway with the synthesis of lactol **3f**.

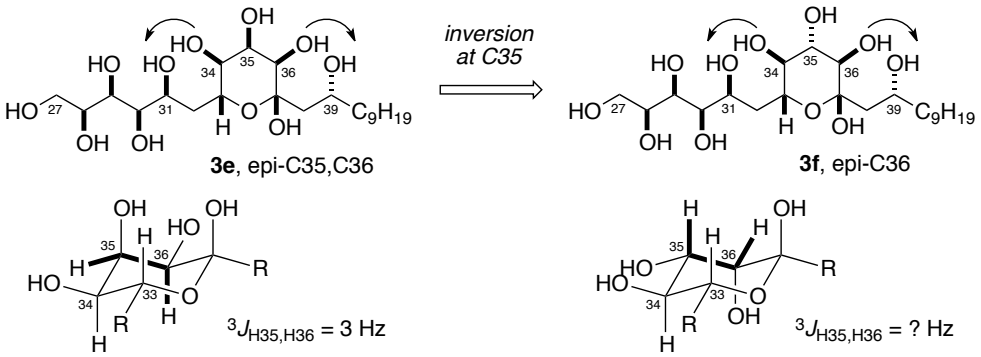
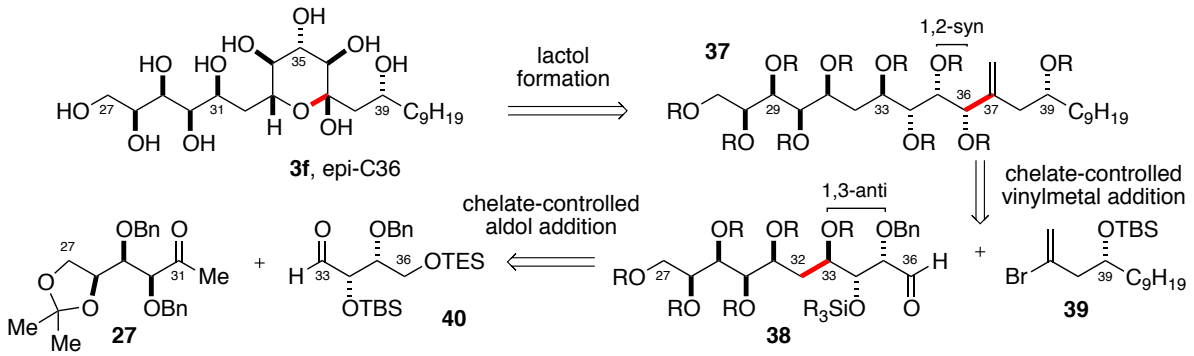


Figure 3.5. Design of epi-C36 lactol **3f** to probe the H35–H36 coupling constant.

C. Synthesis of the epi-C36 Lactol[42]

Our synthesis plan for epi-C36 lactol **3f** relied on the formation of the C36–C37 and C32–C33 bonds by a series of chelation-controlled additions (Scheme 3.11). We began with formation of the C36–C37 bond via 1,2-chelate-controlled addition of the organomagnesiate of vinyl bromide **39** to α-benzyloxy aldehyde **38**.[43] Based upon the Cram chelate model,[36] we expected excellent selectivity for the desired 1,2-syn diastereomer via exclusive formation of a five-membered chelate. Similarly, we expected that addition of ketone **27** to the six-membered chelate of aldehyde **40** would afford the desired 1,3-anti relationship in C27–C36 fragment **38**.

Scheme 3.11. Synthesis plan for epi-C36 lactol **3f**.

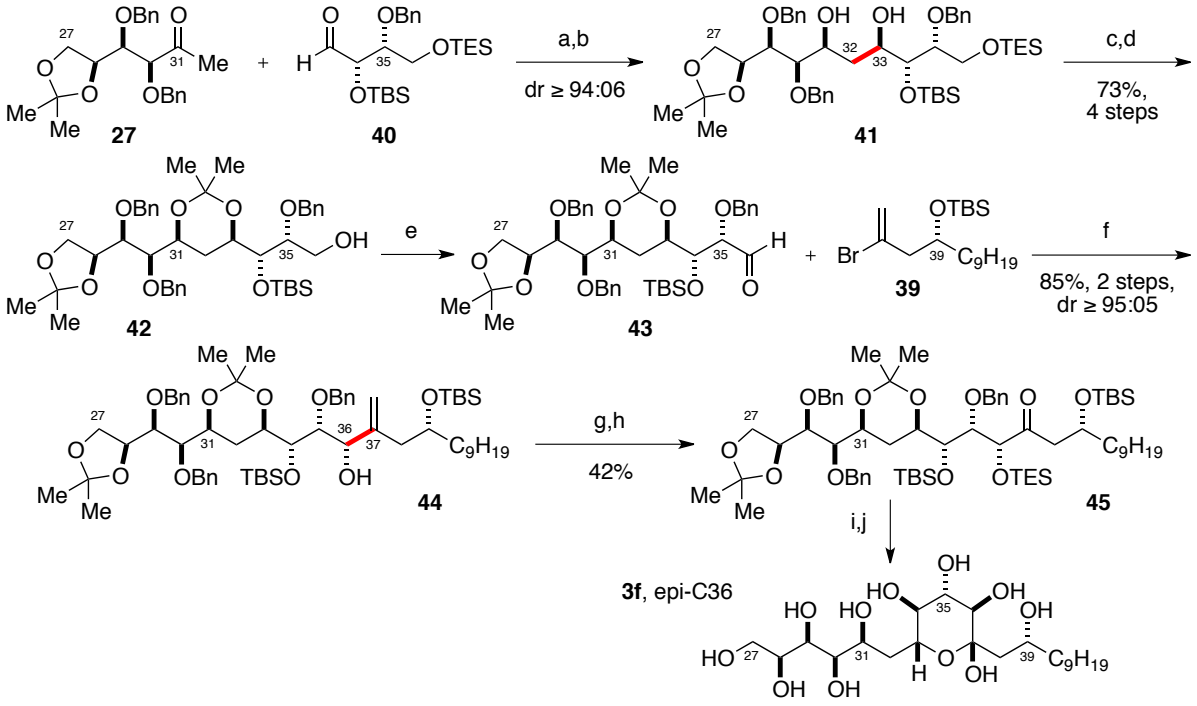


(42) The synthesis of epi-C36 lactol **3f** was achieved by the author in collaboration with Dr. Peter H. Fuller.

(43) For similar chelation-controlled additions of vinylmagnesium reagents, see: (a) Heathcock, C.H.; McLaughlin, M.; Medina, J.; Hubbs, J.L.; Wallace, G.A.; Scott, R.; Claffey, M.M.; Hayes, C.J.; Ott, G.R. *J. Am. Chem. Soc.* **2003**, *125*, 12844–12849; (b) Terrell, L.R. *The Total Synthesis of the Assigned Structure of Amphidinolide A*. Ph.D. Thesis, Michigan State University, **2001**.

The synthesis of lactol **3f** began with the preparation of aldehyde **40** in five steps from cinnamaldehyde[44] (Scheme 3.12). 1,3-Chelation-controlled addition of ketone **27** to aldehyde **40** under soft enolization conditions[4] proceeded with excellent diastereoselection. Prasad reduction[28] of the intermediate adduct furnished diol **41**. Acetonide formation, desilylation and oxidation[17] at C36 yielded aldehyde **43**. Addition of the magnesiated carbanion of vinyl bromide **39**[45] to this aldehyde provided the desired 1,2-syn adduct as a single diastereomer in very good overall yield. Silylation and ozonolysis were followed by the standard deprotection sequence to give epi-C36 lactol **3f**.

Scheme 3.12. Synthesis of epi-C36 lactol **3f**.



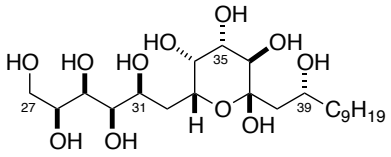
Reagents and conditions: (a) $MgBr_2$•OEt_2, PMP, CH_2Cl_2, –5 °C, dr ≥ 94:06; (b) Et_2BOMe, $NaBH_4$, THF, MeOH, –78 °C to 0 °C; aq H_2O_2, pH 7 buffer, MeOH, 0 °C to rt, dr ≥ 95:05; (c) $Me_2C(OMe)_2$, PPTS, acetone, rt; (d) PPTS, CH_2Cl_2, MeOH, 0 °C to rt, 73% (4 steps); (e) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C; (f) bromide **39**, *t*-BuLi, Et_2O, pentane, –78 °C; $MgBr_2$•OEt_2, Et_2O, PhH, –78 °C to 0 °C; aldehyde **43**, CH_2Cl_2, –78 °C to 0 °C, dr ≥ 95:05, 85% (2 steps); (g) TESCl, imidazole, nBu_4NI, DMF, 0 °C to 60 °C, 73%; (h) O_3, py, CH_2Cl_2, MeOH, –78 °C; PPh_3, –78 °C to rt, 58%; (i) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt, 61%; (c) H_2, Pd black, dioxane, H_2O, rt.

(44) Evans, D.A.; Cee, V.J.; Siska, S.J. *J. Am. Chem. Soc.* **2006**, *128*, 9433–9441.

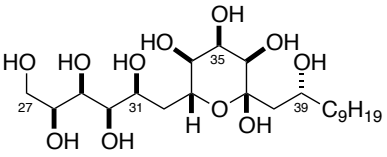
(45) Vinyl bromide **39** may be prepared in two steps from decanal. See: Zhang, Z.; Huang, J.; Ma, B.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3073–3076.

Comparison of the spectroscopic data for lactol **3f** with naturally derived[2] degradation polyol **1** produced a better chemical shift match than lactol **3e** for the H32 methylene protons, but an unexpectedly greater mismatch for the H38 protons (Table 3.5). Full comparison of the three diastereomeric epi-C36 lactols indicated that the absolute configuration of C34 in lactols **3e** and **3f** (as originally assigned) was correct. Unfortunately, chemical shift analysis of the C38 protons was not conclusive regarding the relationship between the C36 and C39 stereocenters. Although we observed a beneficial interchange of H38 resonances across the series, we could never achieve a full spectroscopic profile match for the lactol region of naturally derived[2] degradation fragment **1**. At this point in our search, we judged that we had exhausted all reasonable stereochemical possibilities and decided to discontinue the syntheses of more C27–C48 lactol diastereomers.

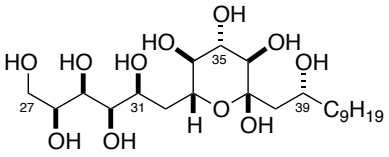
Table 3.5. Chemical shift analysis of C32 and C38 for epi-C36 lactols **3d–f**.[a,b]



3d, epi-C34,C36

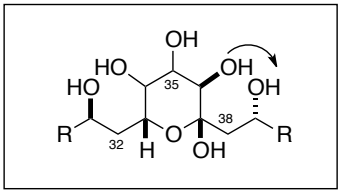


3e, epi-C35,C36



3f, epi-C36

Protons	Sakuda 1	Synthetic 1	Lactol 3d	Lactol 3e	Lactol 3f
H32a	3.17	3.21	2.94	3.09	3.21
H32b	2.49	2.56	2.69	2.51	2.51
H38a	2.45	2.14	2.64	2.45	2.67
H38b	2.19	2.73	2.05	2.16	2.06



[a] All chemical shifts (δ) are reported in ppm. [b] Measured in pyridine-d_5.

IV. A Solution to the Structural Problem[46]

Despite achieving the syntheses of model C27–C48 lactol **3a** and five of its diastereomers (**3b–3f**), we were left without a suitable spectroscopic match for naturally derived[2] C3–C48 degradation product (née "lactol") **1**. Prior comparisons of proton chemical shift data left the relationship between the C33–C37 lactol and the isolated C39 stereocenter unclear, so we shifted focus to the chemical shift of the C37 lactol carbon.

Having believed the structural issue to be stereochemical in origin for so long, we were delighted to realize that our data for the C37 lactol carbon of model C27–C48 lactol **3a** closely matched that reported for the C35 lactol carbon of the structurally related blasticidin A (BcA) C3–C47 degradation lactol **47** (Table 3.6).[47] Generally speaking, the chemical shift of the C37 carbon in all model C27–C48 diastereomers more closely matched that of the BcA C35 lactol carbon than the C37 carbon of naturally derived[2] AsA C3–C48 degradation product **1**. Furthermore, literature data for the C37 carbon of naturally derived AsA degradation product **1** closely matched that reported for the BcA degradation lactol methyl ether **48**.[47,48]

These observations prompted us to formally convert model C27–C48 lactol **3a** to its lactol methyl ether **51a** (Scheme 3.13). The synthesis of model C27–C48 lactol methyl ether **51a** was accomplished in four steps from aldol adduct **49**. Removal of the acetonide and silyl protecting groups was interrupted to ease the subsequent purification of lactol methyl ether **50**. Cleavage of the C36 TBS ether was followed by debenzylation to give lactol methyl ether **51a**.

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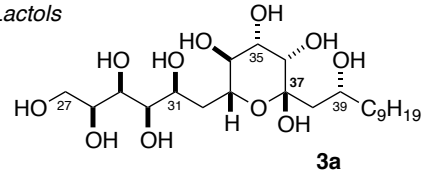
(46) The solution to the structural problem was discovered by the author in collaboration with Dr. Peter H. Fuller.

(47) Sakuda, S.; Ikeda, H.; Nakamura, T.; Kawachi, R.; Kondo, T.; Ono, M.; Sakurada, M.; Inagaki, H.; Ito, R.; Nagasawa, H. *J. Antibiotics* **2000**, *53*, 1378–1384.

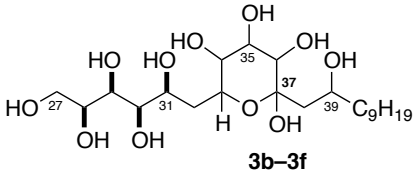
(48) For a complete comparison of tabulated spectral data for naturally derived and synthetic AsA C3–C48 degradation lactols **1**, see: Appendix 1.

Table 3.6. Chemical shift analysis of AsA C37 (BcA C35) for lactols and lactol methyl ethers.[a]

Model C27–C48 Lactols

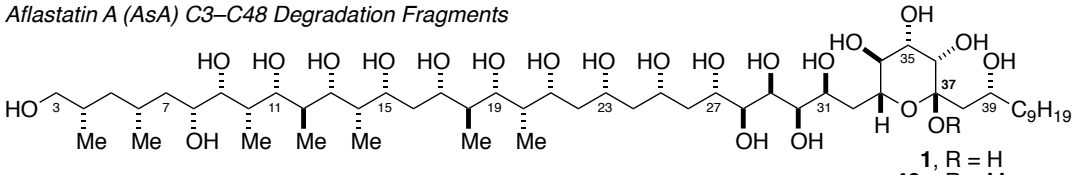


3a



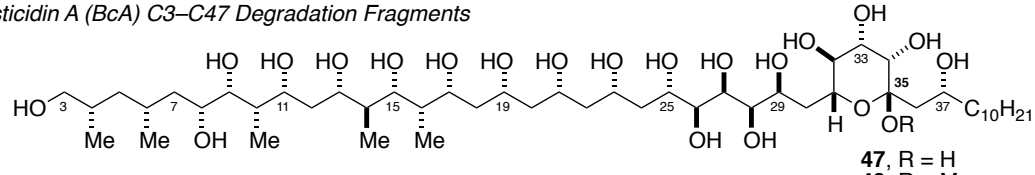
3b–3f

Aflastatin A (AsA) C3–C48 Degradation Fragments



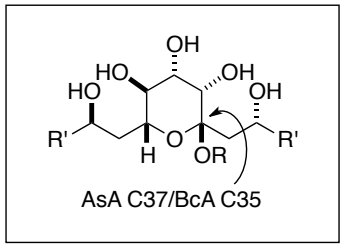
1, R = H
46a, R = Me

Blasticidin A (BcA) C3–C47 Degradation Fragments



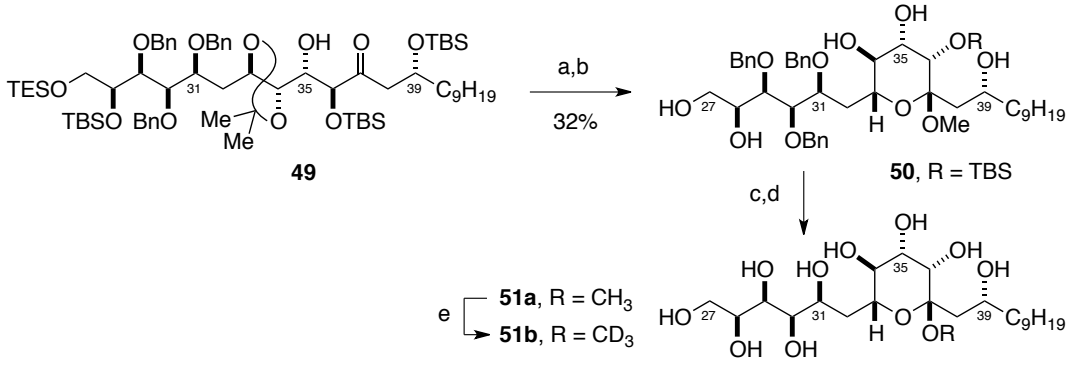
47, R = H
48, R = Me

Group	Carbon	Lactol(s)	R	δ (ppm)
Evans	AsA C37	**3a**	H	100.2
	AsA C37	**3b–3f**	H	99.8–100.8[b]
	AsA C37	**1**	H	101.2[c]
Sakuda	AsA C37	**1**	"H"	103.2
	BcA C35	**47**	H	100.1
	BcA C35	**48**	Me	103.3



[a] Measured in pyridine-d_5. [b] Average δ = 100.2 ppm. [c] Later corrected to δ = 100.1 ppm.

Scheme 3.13. Syntheses of model C27–C48 lactol methyl ethers **51a** and **51b**.



49

50, R = TBS

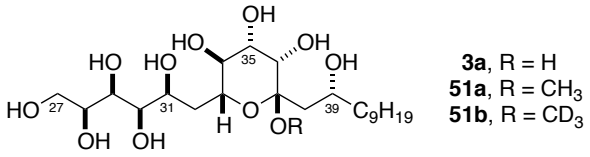
Reagents and conditions: (a) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt, 50%; (b) PPTS, CH_2Cl_2, MeOH, rt, 63%; (c) nBu_4NF, THF, 0 °C; TMSOMe; (d) H_2, Pd black, dioxane, H_2O, rt; (e) Dowex 50x8 (H^+), CD_3OD, rt.

The chemical shift of the C37 carbon of model C27–C48 lactol methyl ether **51a** correlated nicely with that reported for naturally derived[2] AsA C3–C48 degradation product **1**

(Table 3.7). We then became curious why the resonances belonging to the newly incorporated methyl group were absent from their NMR spectra of naturally derived degradation product **1**. We hypothesized that during the course of their NMR spectroscopic studies,[2a] the isolation group dissolved AsA degradation lactol methyl ether **46a** in methanol-d_4 and inadvertently exchanged the methyl ether for its trideuteriomethyl ether (**46b**). To substantiate this proposal, we converted model lactol methyl ether **51a** to trideuteriomethyl ether **51b** in the presence of trace acid (Dowex) (Scheme 3.13).

Table 3.7. Chemical shift analysis of AsA C37 for model lactol **3a**, lactol methyl ethers **51a** and **51b**, and degradation fragment **1**.[a]

Group	Lactol	R	δ (ppm)
Evans	**3a**	H	100.2
	51a	CH_3	103.3
	51b	CD_3	103.3
Sakuda	**1**	"H"	103.2



3a, R = H
51a, R = CH_3
51b, R = CD_3

[a] Measured in pyridine-d_5.

As expected, the chemical shift of the C37 carbon of model lactol trideuteriomethyl ether **51b** correlated nicely with that reported for naturally derived AsA C3–C48 degradation product **1** (Table 3.7). In fact, model lactol ethers **51a** and **51b** were spectroscopically indistinct with the exception of the obvious resonances. Furthermore, the spectroscopic data for lactol trideuteriomethyl ether **51b** provided us the best profile match for naturally derived degradation fragment **1** in the C27–C48 lactol region (Figure 3.6). The only data point that concerned us was the chemical shift of C36, but resolution of this difference between the two structures will be discussed in due course.

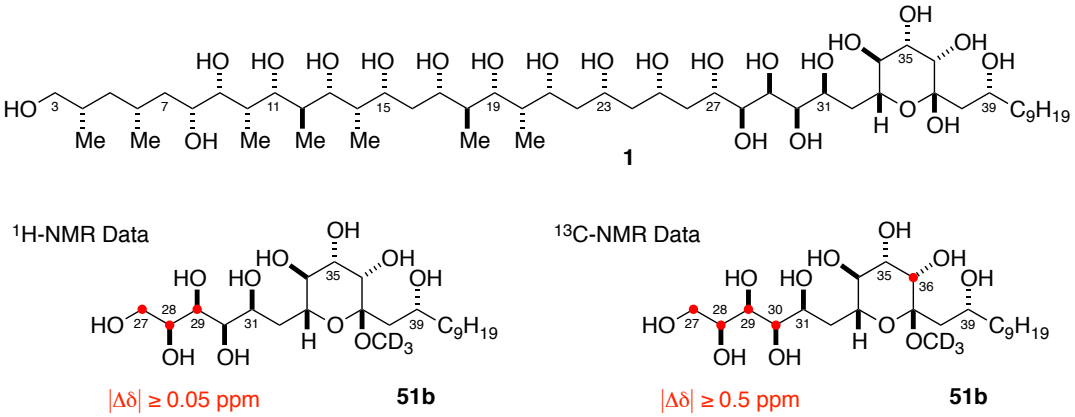
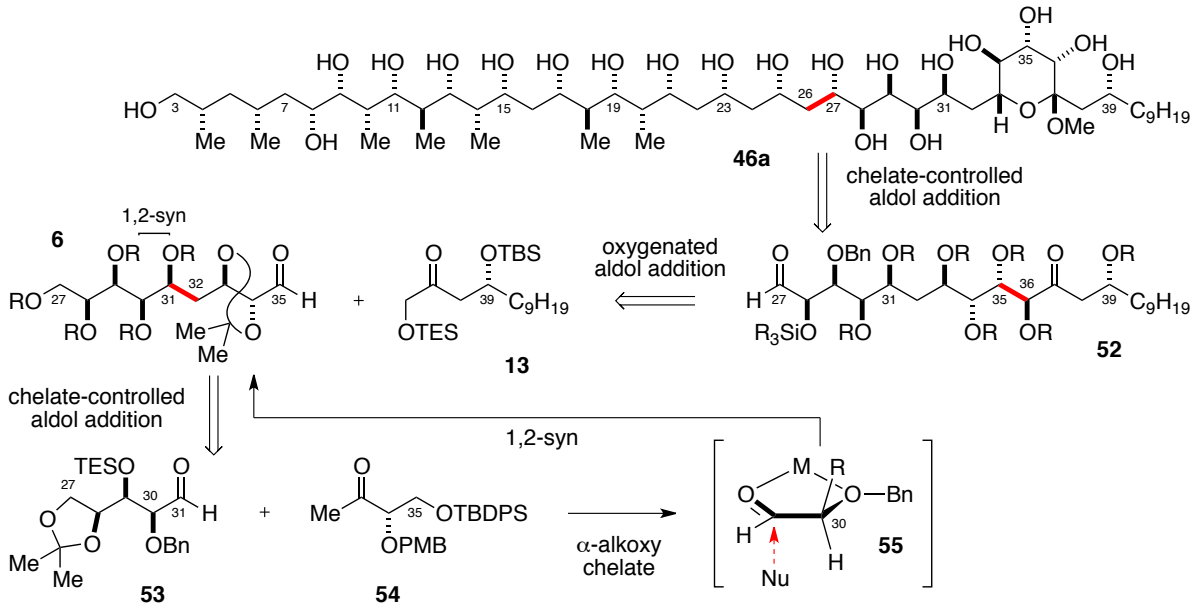


Figure 3.6. NMR data comparison of naturally derived C3–C48 degradation lactol **1** to model C27–C48 lactol trideuteriomethyl ether **51b**.

V. Syntheses of the C3–C48 Degradation Fragments

Now confident that we had found a solution to our structural problem, we pursued the syntheses of AsA C3–C48 degradation lactol methyl ether **46a** and its trideuteriomethyl ether analogue (**46b**). Rather than retrace the route we had originally used to synthesize C3–C48 degradation lactol **1**, we decided to modify our synthesis plan for C27–C48 aldehyde **52** (Scheme 3.14). We began with the usual C35–C36 aldol bond disconnection[13] to produce C27–C35 aldehyde **6** and C36–C48 ketone **13**. In this iteration, we decided to install a triethylsilyl ether at the C36 carbinol position of ketone **13**,[24] as we had in the synthesis of epi-C33–C37 lactol **3c**, to facilitate global deprotection. Then, given the success of our newly developed 1,3-chelate-controlled aldol reaction, we anticipated extending our soft enolization-based method[4] to the formation of the C31–C32 bond via 1,2-chelate-controlled addition of ketone **54** to aldehyde **53**. Based upon the Cram chelate model,[36] we expected excellent selectivity for the desired 1,2-syn diastereomer via exclusive formation of five-membered chelate **55** and nucleophilic addition to the less sterically hindered face.

Scheme 3.14. Synthesis plan for C3–C48 degradation fragment **46a**.



The synthesis of C27–C35 aldehyde **53**[49] commenced with the glycolate aldol addition of oxazolidinone **57**[50] to aldehyde **56**,[51] which afforded the desired syn adduct **58** in good yield and excellent diastereoselectivity (Scheme 3.15). Silylation and net reduction afforded α-benzyloxyaldehyde **53** in good overall yield. Chelate-controlled addition of C32–C35 ketone **54**[52] to this C27–C31 aldehyde under our soft enolization conditions delivered the desired β-hydroxy ketone **59** on multigram scale.[53] As before, our magnesium-promoted aldol process was found to exhibit exceptionally high asymmetric induction.[27,54] Diastereoselective

(49) The synthesis of C27–C35 aldehyde **67** was first achieved by Dr. Egmont Kattnig using a chelation-controlled/soft enolization-based approach. The synthesis of C27–C48 aldehyde **71** from redesigned C36–C48 ketone **13** was then completed by the author in collaboration with Dr. Peter H. Fuller (*vide infra*).

(50) Evans, D.A.; Gage, J.R.; Leighton, J.L.; Kim, A.S. *J. Org. Chem.* **1992**, *57*, 1961–1963.

(51) Aldehyde **56** was prepared in two steps from L-gulonic acid γ-lactone. See: Hubschwerlen, C.; Specklin, J.-L.; Higelin, J. *Org. Synth.* **1995**, *72*, 1–5.

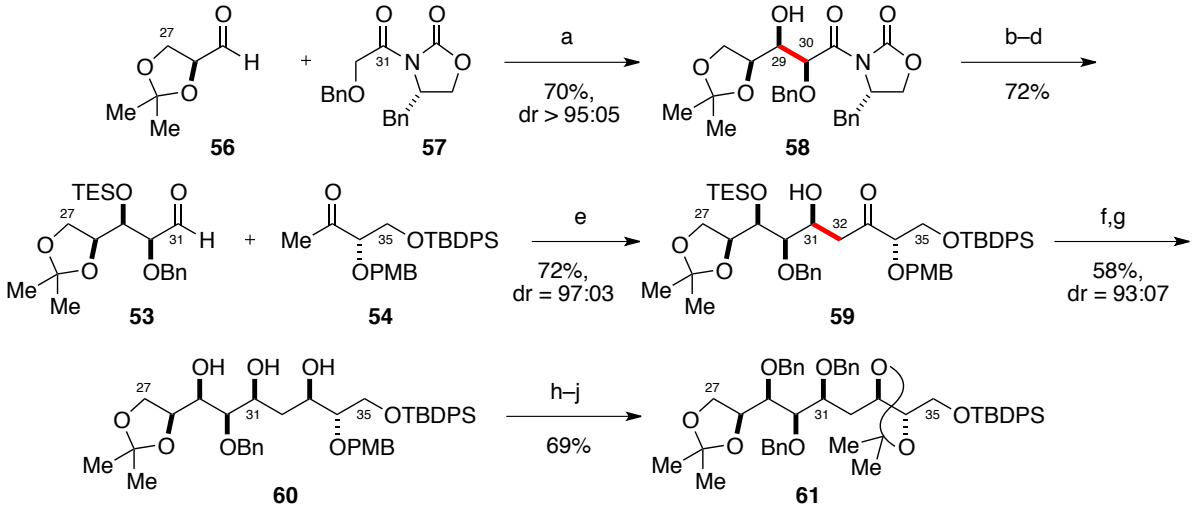
(52) Ketone **54** was prepared in six steps from L-serine. See: Hirth, G.; Walther, W. *Helv. Chim. Acta* **1985**, *68*, 1863–1871.

(53) Chelate-controlled Mukaiyama aldol addition of the corresponding enolsilane of ketone **54** to aldehyde **53** was again unsuccessful.

(54) To make a more efficient synthesis, we would prefer to protect the C29 oxygen as its benzyl ether, but reaction of the corresponding aldehyde with ketone **54** under our soft enolization conditions produced an

carbonyl reduction[55] was followed by desilylation to produce triol **60**. Installation of the C33,C34 acetonide to produce the fully protected C27–C35 fragment **61** required three protecting group manipulations: PMP acetal formation,[56] dibenzylation, and acetal exchange.

Scheme 3.15. Synthesis of C27–C35 fragment **61**.



Reagents and conditions: (a) $(nBu)_2BOTf$, Et_3N, PhMe, –78 °C to –40 °C, dr > 95:05, 70%; (b) TESCl, imidazole, DMF, rt, 84%; (c) $LiBH_4$, H_2O, THF, 0 °C to rt, 92%; (d) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –40 °C to –10 °C, 93%; (e) $MgBr_2$•OEt_2, PMP, CH_2Cl_2, –5 °C, dr = 97:03, 72%; (f) $Zn(BH_4)_2$, CH_2Cl_2, Et_2O, –78 °C, dr = 93:07, 86%; (g) PPTS, CH_2Cl_2, MeOH, 0 °C, 68%; (h) DDQ, 4 Å MS, CH_2Cl_2, 0 °C, 83%; (i) BnBr, NaH, nBu_4NI, THF, 0 °C to rt, 88%; (j) $Me_2C(OMe)_2$, PPTS, acetone, 55 °C, 95%.

Alternatively, the fully protected C27–C35 fragment **61** may be accessed from dibenzylglucopyranoside **62**[57] in twelve steps (Scheme 3.16). Iodination,[58] zinc-mediated fragmentation,[59] *in situ* reduction, and protection of the resultant 1,2-diol produced acetonide **63** in good overall yield. Ozonolysis and stereoselective allylation of the resultant syn α,β-bisalkoxy aldehyde produced homoallylic alcohol **64** in moderate yield. We also observed a

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unfavorable mixture of diastereomers (dr = 49:51), whereas allylmagnesium bromide addition produced homoallylic carbinol **64** in very good diastereoselectivity (dr = 89:11) (*vide infra*).

(55) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338–344 and references therein.

(56) Oikawa, Y.; Nishi, T.; Yonemitsu, O. *Tetrahedron Lett.* **1983**, *24*, 4037–4040.

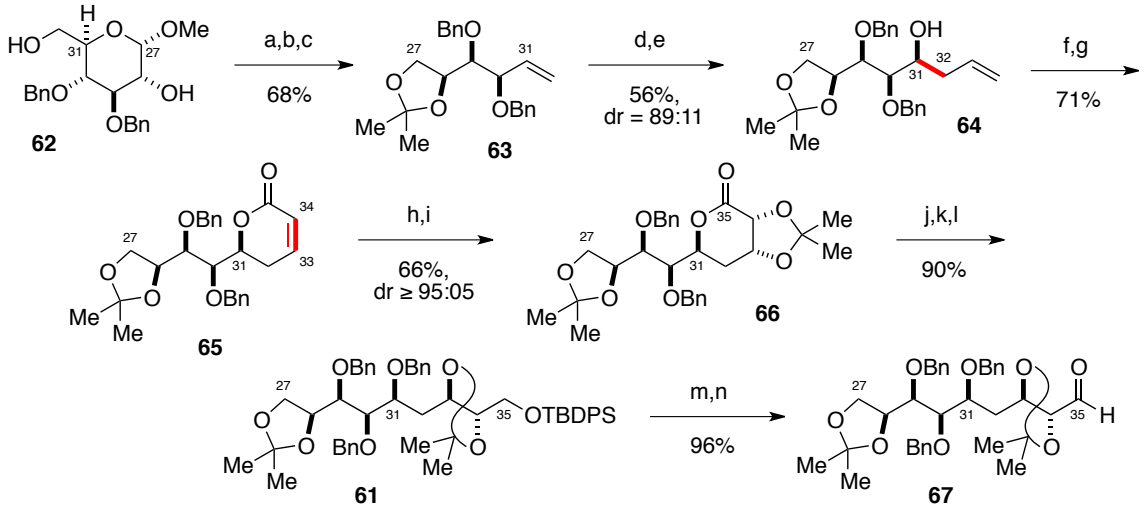
(57) Français, A.; Urban, D.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8662–8665.

(58) (a) Garegg, P.J.; Samuellson, B. *J. Chem. Soc., Perkin Trans. I.* **1980**, 2866–2869; (b) Garegg, P.J.; Johansson, R.; Ortega, C.; Samuellson, B. *J. Chem. Soc., Perkin Trans. I.* **1982**, 681–683.

(59) Skaanderup, P.R.; Hyldtoft, L.; Madsen, R. *Monatsh. Chem.* **2002**, *133*, 467–472.

diminished level of diastereoselection (dr = 89:11) when compared to our previous synthesis in which the aldehyde substrate had silyl protecting groups at C27 and C28. Acryloylation[60] of the nascent C31 carbinol, and ring-closing metathesis[61] of the intermediate diene then furnished unsaturated lactone **65**. Stereoselective dihydroxylation[62,63] and acetonide formation produced lactone **66** as a single diastereomer. Reduction to the diol, selective protection of the primary carbinol, and benzylation yielded common intermediate **61**. Desilylation and oxidation[17] of the resultant carbinol ultimately provided C27–C35 aldehyde **67**.

Scheme 3.16. Alternative synthesis of C27–C35 aldehyde **67**.



Reagents and conditions: (a) PPh_3, I_2, imidazole, PhMe, MeCN, rt, 97%; (b) Zn, THF, H_2O,))), 45 °C; $NaBH_4$, 0 °C, 78%; (c) $Me_2C(OMe)_2$, PPTS, acetone, rt, 90%; (d) O_3, py, CH_2Cl_2, MeOH, –78 °C; PPh_3, –78 °C to rt; (e) $MgBr_2$•OEt_2, allylMgBr, CH_2Cl_2, Et_2O, –78 °C to –40 °C, dr = 89:11, 56% (2 steps); (f) acrylic pivalic anhydride, $EtN(iPr)_2$, DMAP, THF, PhH, rt, 80%; (g) $(Ph_3P)_2Cl_2Ru$=CHPh (4 x 5 mol%), PhH, 65 °C, 89%; (h) $RuCl_3$, $CeCl_3$•$7H_2O$, $NaIO_4$, EtOAc, MeCN, H_2O, 0 °C, 85%, dr ≥ 95:05; (i) $Me_2C(OMe)_2$, PPTS, acetone, 30 °C, 78%; (j) $LiBH_4$, H_2O, THF, 0 °C to rt, quant.; (k) TBDPSCl, imidazole, DMF, 0 °C, 95%; (l) BnBr, NaH, nBu_4NI, DMF, –20 °C, 95%; (m) nBu_4NF, THF, 0 °C, quant.; (n) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C, 96%.

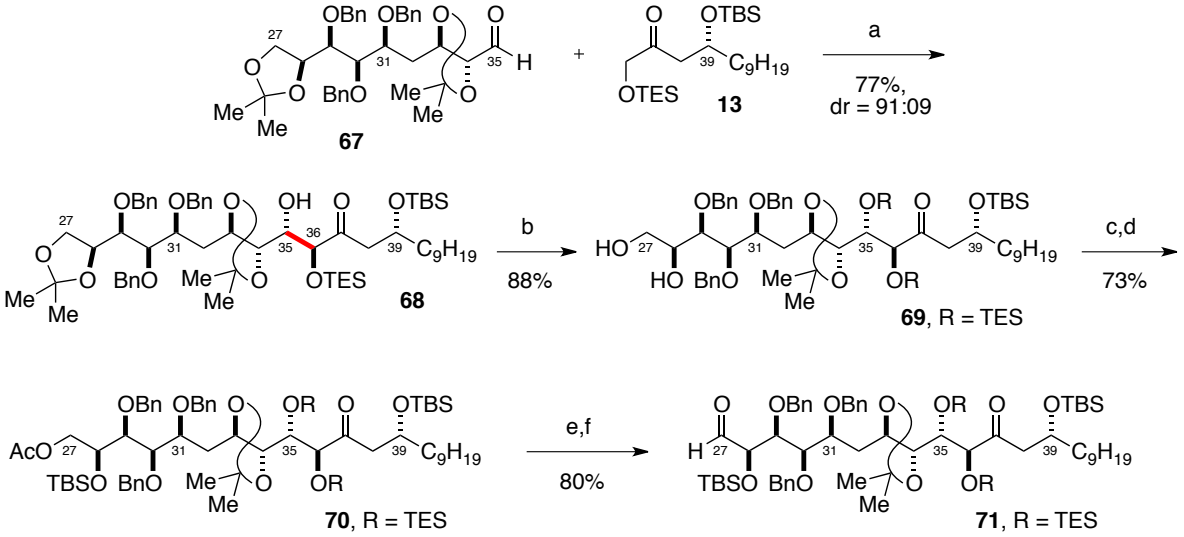
(60) Tanaka, A.; Suzuki, H.; Yamashita, K. *Agric. Biol. Chem.* **1989**, *53*, 2253–2256.

(61) Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R.H. *Angew. Chem.* **1995**, *107*, 2179–2181; *Angew. Chem., Int. Ed.* **1995**, *34*, 2039–2041.

(62) (a) Plietker, B.; Niggemann, M. *J. Org. Chem.* **2005**, *70*, 2402–2405; (b) Plietker, B. *Synthesis* **2005**, 2453–2472.

(63) For examples of the diastereoselective dihydroxylation of related α,β-unsaturated δ-lactones using Upjohn conditions (OsO_4, NMO), see: (a) Ghosh, A.K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 3967–3969; (b) Ramachandran, P.V.; Prabhudas, B.; Chandra, J.S.; Reddy, M.V.R. *J. Org. Chem.* **2004**, *69*, 6294–6304; (c) Bhaket, P.; Stauffer, C.S.; Datta, A. *J. Org. Chem.* **2004**, *69*, 8594–8601.

Scheme 3.17. Synthesis of C27–C48 aldehyde **71**.



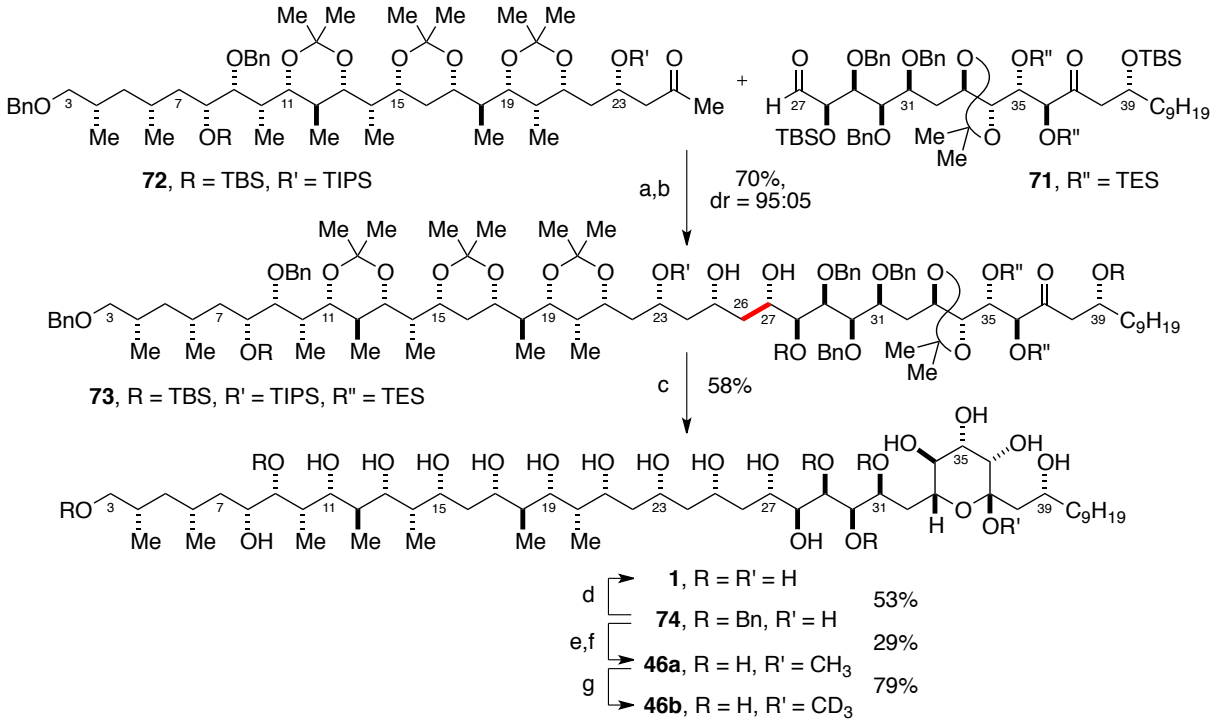
Reagents and conditions: (a) ketone **13**, Cy_2BCl, Me_2NEt, pentane, 0 °C to rt; aldehyde **67**, Et_2O, –78 °C to –25 °C, dr = 91:09, 77%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; TMSOTf; aq H_2SO_4, 88%; (c) AcCl, 2,4,6-collidine, CH_2Cl_2, –78 °C to 0 °C, 98%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 74%; (e) DIBALH, CH_2Cl_2, –78 °C, 84%; (f) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C, 95%.

Having completed the syntheses of both the C3–C26 and C27–C48 fragments, we ventured forward with the key aldol coupling (Scheme 3.18).[64] Satisfyingly, chelate-controlled addition of ketone **72** to aldehyde **71** under our soft enolization conditions[4] delivered the desired β-hydroxy ketone with excellent diastereoselection. We immediately reduced the aldol adduct[65] under Prasad's conditions[28] to afford 1,3-syn diol **73** as a single diastereomer in good overall yield. Both steps were completely chemoselective and eliminated the need to mask the C37 carbonyl.

(64) The syntheses of the C3–C48 degradation fragments were achieved by the author in collaboration with Dr. Peter H. Fuller.

(65) We observed that the intermediate aldol adduct is subject to retro-aldolization on silica gel. For higher overall yields of diol **73**, we performed the aldol addition and reduction in tandem before purification.

Scheme 3.18. Synthesis of C3–C48 degradation fragments **1**, **46a**, and **46b**.



Reagents and conditions: (a) $MgBr_2$•OEt_2, PMP, CH_2Cl_2, –5 °C, dr = 95:05; (b) Et_2BOMe, $NaBH_4$, THF, MeOH, –78 °C to –55 °C; aq H_2O_2, aq NaOH, MeOH, 0 °C, dr ≥ 95:05, 70% (2 steps); (c) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt, 58%; (d) H_2, Pd black, dioxane, H_2O, rt, 53%; (e) Dowex 50x8 (H^+), MeOH, 30 °C, 39%; (f) H_2, Pd black, dioxane, H_2O, rt, 74%; (g) Dowex 50x8 (H^+), CD_3OD, rt, 79%.

We concluded the synthesis of C3–C48 degradation lactol methyl ether **46a** in three steps from diol **73**. As before, removal of the acetonide and silyl protecting groups was best achieved with hexafluorosilicic acid.[66] We obtained pentabenzyl ether **74** in higher yield and purity than previously due to the increased lability of the C36 triethylsilyl ether. The nascent lactol was then converted to its lactol methyl ether, and the remaining benzyl ethers cleaved to unveil C3–C48 degradation lactol methyl ether **46a** in modest yield. Transetherification of lactol methyl ether **46a** was performed in the presence of methanol-d_4 and trace acid (Dowex) to afford C3–C48 trideuteriomethyl ether **46b** in good yield. Finally, we achieved our second synthesis of C3–C48 degradation fragment **1** in two steps and better overall yield from pentabenzyl ether **74** via the standard two-step deprotection sequence.

(66) (a) Pilcher, A.S.; Hill, D.K.; Shimshock, S.J.; Waltermire, R.E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492–2495; (b) Pilcher, A.S.; Shimshock, S.J. *J. Org. Chem.* **1993**, *58*, 5130–5134.

VI. Spectroscopic Analysis of the C3–C48 Degradation Fragments[67]

Upon completion of the syntheses of degradation fragments **1**, **46a**, and **46b** (Figure 3.7), we proceeded with their full spectroscopic analysis. Our data for lactol trideuteriomethyl ether **46b** correlated nicely with those tabulated for naturally derived[2] degradation product **1**. All chemical shift values in the proton and carbon spectra were within 0.03 ppm and 0.2 ppm of each other, respectively, with one caveat. In conjunction with the stereochemical revision of AsA, the chemical shift of C25 of naturally derived degradation product **1** was revised from 73.1 ppm to 71.1 ppm.[2b] However, our data for model C27–C48 lactol trideuteriomethyl ether **46b** indicated that the value of 73.1 ppm should be assigned to C36. As a result, we believe the chemical shift value of 71.5 ppm originally reported for C36 should instead be revised to 71.1 ppm. Then, the carbon data for these two atoms, as well as the proton data for H25 and H36, should be switched. We believe this error resulted from misinterpretation of two-dimensional NMR correlation (i.e. COSY, HMQC, and HMBC) data,[2a] as the proton signals are very close in chemical shift. Our proposed correction is supported by the corresponding data for BcA C3–C47 degradation lactol methyl ether **48**.[47] Upon making this correction, we make two important conclusions:

*1) The data reported by the isolation group for naturally derived AsA C3–C48 degradation lactol **1** should in fact be attributed to its derivative lactol trideuteriomethyl ether **46b**; and*

*2) Our synthesis of lactol trideuteriomethyl ether **46b** and its spectroscopic match to naturally derived C3–C48 degradation fragment **1** confirm the revised stereochemical assignment of AsA.*

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(67) The spectroscopic analysis of C3–C48 degradation lactol **1** was first performed by Dr. Egmont Kattnig and later revised by the author. The spectroscopic analyses of C3–C48 degradation lactol methyl ethers **46a** and **46b** were performed by the author in collaboration with Dr. Peter H. Fuller.

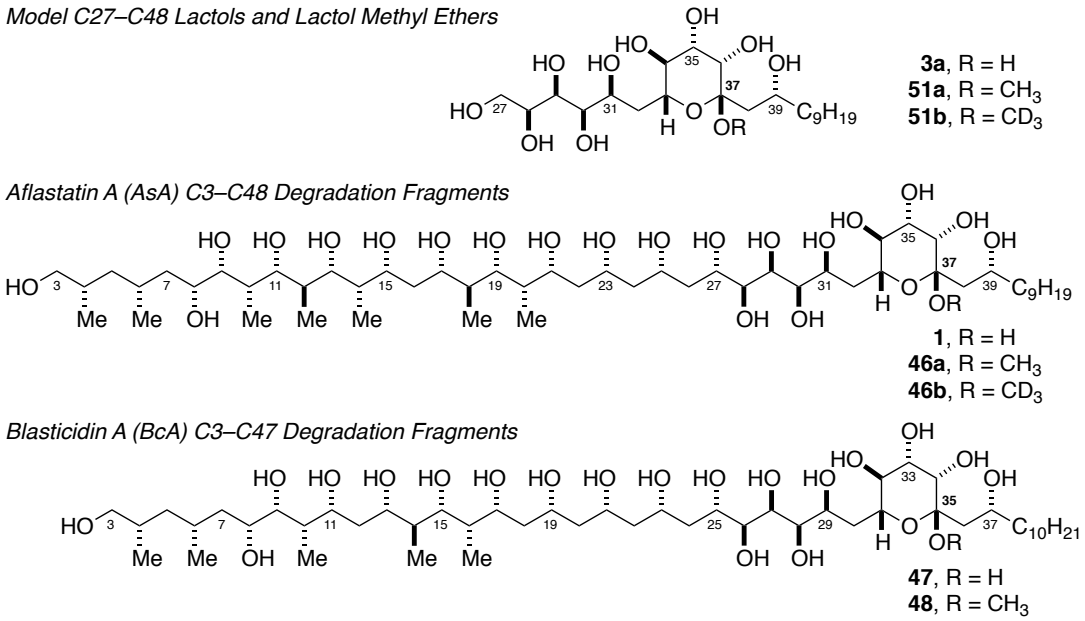


Figure 3.7. Structures of AsA model lactol **3a**, model lactol methyl ethers **51a** and **51b**, C3–C48 degradation fragments **1**, **46a**, and **46b**, and BcA C3–C47 degradation fragments **47** and **48**.

In continuation of our analysis, the data for trideuteriomethyl ether **46b** and lactol methyl ether **46a** were spectroscopically indistinct with the exception of the obvious resonances. By extension, our data for lactol methyl ether **46a** also matched naturally derived[2] degradation product **1** apart from the resonances belonging to the methyl group. We hypothesized that during the course of their NMR spectroscopic studies, the isolation group dissolved degradation fragment **46a** (née **1**) in methanol-d_4 and inadvertently exchanged the methyl ether for its trideuteriomethyl ether **46b** in the presence of trace acid.[68] Our hypothesis is reasonable because structural elucidation of the corresponding AsA C9–C27 degradation fragment was conducted in methanol-d_4 or a mixture of methanol-d_4 and pyridine-d_5. Unfortunately, we have no evidence that C3–C48 degradation lactol methyl ether **46a** was ever dissolved in methanol-d_4 because the NMR spectra are reported in pyridine-d_5.

(68) In our hands, simple filtration of model C27–C48 lactol methyl ether **51a** through Dowex 50x8 (H^+) resin and dissolution in methanol-d_4 resulted in little to no ether exchange (<10% conversion to lactol trideuteriomethyl ether **51b** by ^{1}H-NMR over one week at room temperature).

We explicitly propose that the isolation group synthesized lactol trideuteriomethyl ether **46b** by transetherification of lactol methyl ether **46a**, which we noted is experimentally more facile in the presence of trace acid (Dowex) than the ketalization of parent lactol **1**. As a result, we suspect that the isolation group did not synthesize aflastatin A C3–C48 degradation lactol **1** as reported. Our notion is supported by inconsistencies between experimental procedures disclosed for the degradations of AsA and BcA to their respective lactols **1** and **47**. In the case of AsA, the last reported chemical step is the saponification of the peracetate of lactol **1**, followed by neutralization of the crude product mixture by passing it through an acidic Dowex column. In the case of BcA, saponification was performed on the peracetate of lactol methyl ether **48**, and hydrolysis of lactol methyl ether **48** to its parent lactol **47** required an extra step, namely exposure to strong aqueous acid. We expect that the hydrolysis of AsA C3–C48 degradation lactol methyl ether **46a** to its corresponding lactol **1** requires similar acidic conditions. In the end, we suspect that lactol trideuteriomethyl ether **46b** was mistaken for lactol **1** upon acquisition of NMR spectra that lacked resonances corresponding to the proper product, lactol methyl ether **46a**.

The NMR data that we present for AsA C3–C48 degradation product **1** is the first to be reported for this structure. Our second synthesis of this structure allowed us to revise our own chemical shift data for the C37 carbon from 101.2 ppm to 100.1 ppm, thus bringing it into excellent agreement with model C27–C48 lactol **3a** and BcA C3–C47 degradation lactol **47** (Table 3.6). Overall, our NMR data for AsA C3–C48 degradation lactol **1** may best be described as a rough overlay of the C3–C27 and C40–C48 regions of naturally derived AsA C3–C48 degradation fragment **46a** (née **1**) and the C20–C41 (or C22–C43 by AsA numbering) region of BcA C3–C47 degradation lactol **47** (Appendix 1, Tables 7 and 8). As

such, we are confident that our data for AsA C3–C48 degradation product **1** is correct and not attributable to any other structure.

As final proof of structure, the high-resolution mass spectrometry (HRMS) data that we measured for AsA C3–C48 degradation lactol **1** predicts the correct molecular formula, $C_{53}H_{106}O_{22}$. Although this result was expected, we could not explain Sakuda's matching HRMS data for naturally derived degradation fragment **1**, which we structurally reassigned as lactol trideuteriomethyl ether **46b**. Looking to resolve this issue, we scrutinized their published spectra for any recognizable amount of lactol **1**, but only observed a lopsided mixture of lactol trideuteriomethyl and lactol methyl ethers **46b** and **46a**, respectively.[69] We then tested the possibility that HRMS data for lactol **1** could be obtained from such a mixture. We succeeded, but were unable to reproduce the accuracy of the isolation group's measurement.[70]

At the conclusion of our spectroscopic analyses, we had successfully revised the structure of the naturally derived AsA C3–C48 degradation fragment from lactol **1** to its lactol trideuteriomethyl ether derivative **46b**. We believe that the misassignment of this fragment provided us the opportunity to test structural curiosities while displaying the true power of chemical synthesis. In particular, our accumulated work involving soft enolization with magnesium clearly demonstrated the reliability of our chelate-controlled aldol method in complex settings, as well as its potential applicability to the large-scale production of chiral

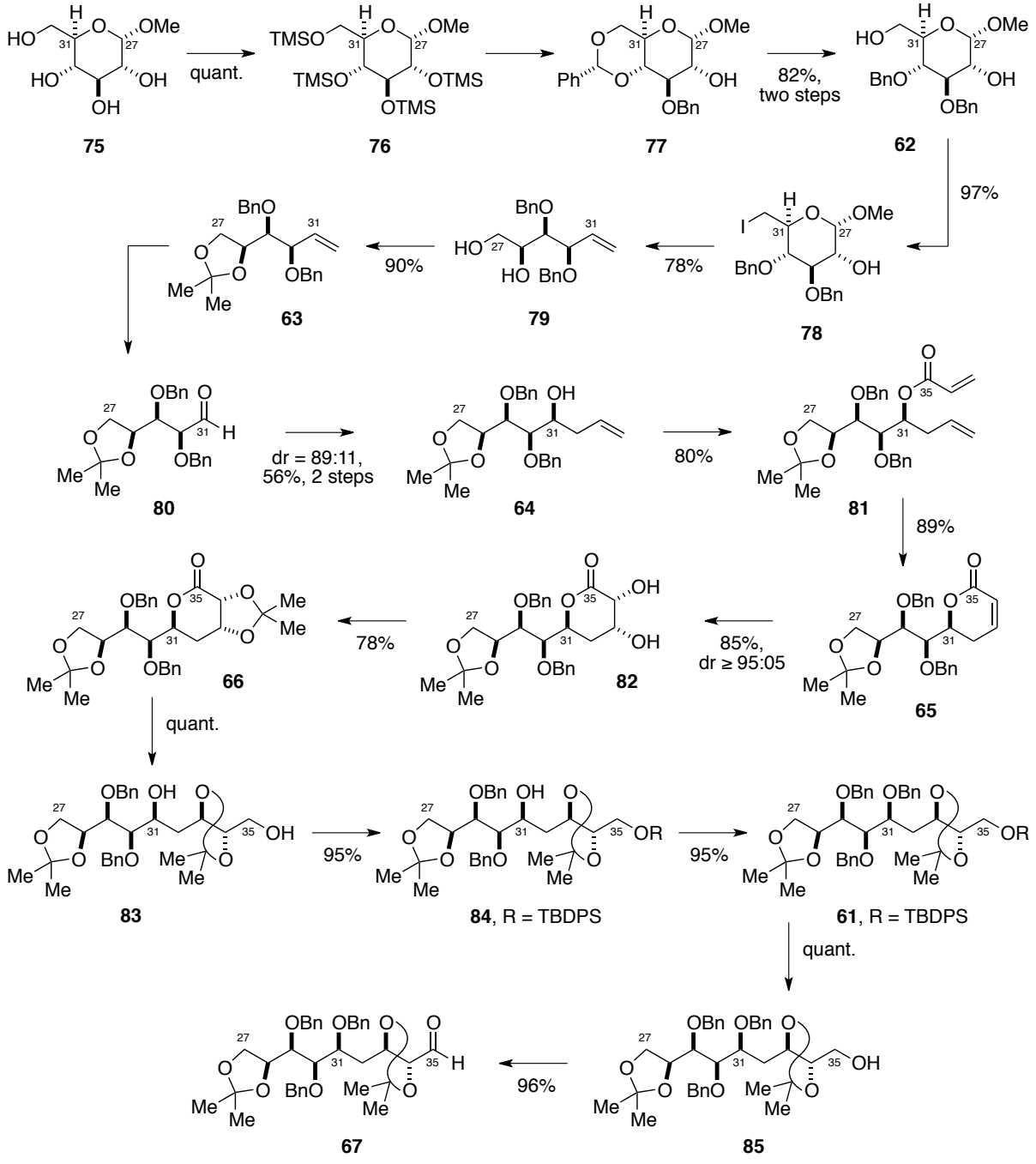
(69) The tabulated NMR data for degradation product **1** (Ref. 2a) is devoid of resonances corresponding to the methyl group of lactol methyl ether **46a**. However, these resonances appear to be attenuated in the published spectra. Therefore, spectral analysis was presumably completed on some mixture of lactol methyl and lactol triodeuteriomethyl ethers **46a** and **46b**, respectively.

(70) High-resolution mass spectrometry (HRMS) data corresponding to lactol **1** (*m/z* calcd for $C_{53}H_{106}NaO_{22}$ $[M+Na]^+$: 1117.7068) may be obtained from a sample containing lactol methyl ether **46a** (TOF, found: 1117.7279) or lactol trideuteriomethyl ether **46b** (TOF, found: 1117.7353). As such, we believe it possible that MS data corresponding to degradation lactol **1** (Ref. 2a) may be obtained from a mixture of lactol methyl ether **46a** and its derivative lactol trideuteriomethyl ether **46b**.

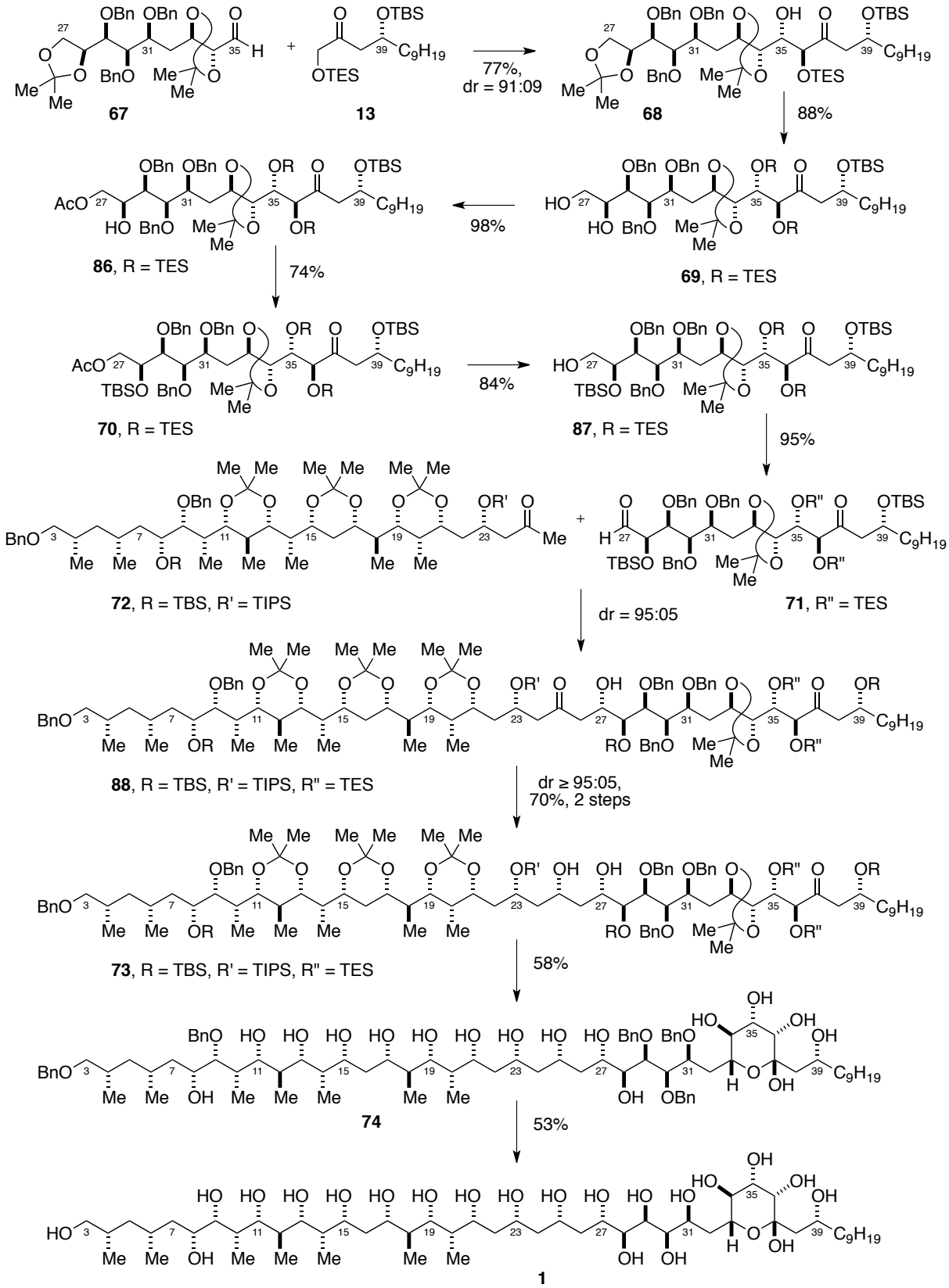
building blocks for stereoselective organic synthesis. Now, with the syntheses of the AsA degradation fragments behind us, and the structural revision duly confirmed, we were ready to tackle the synthesis of the natural product. Our work toward the installation of the tetramic acid and the completion of the total synthesis of aflastatin A will be discussed in Chapter 4.

VII. Graphical Summary

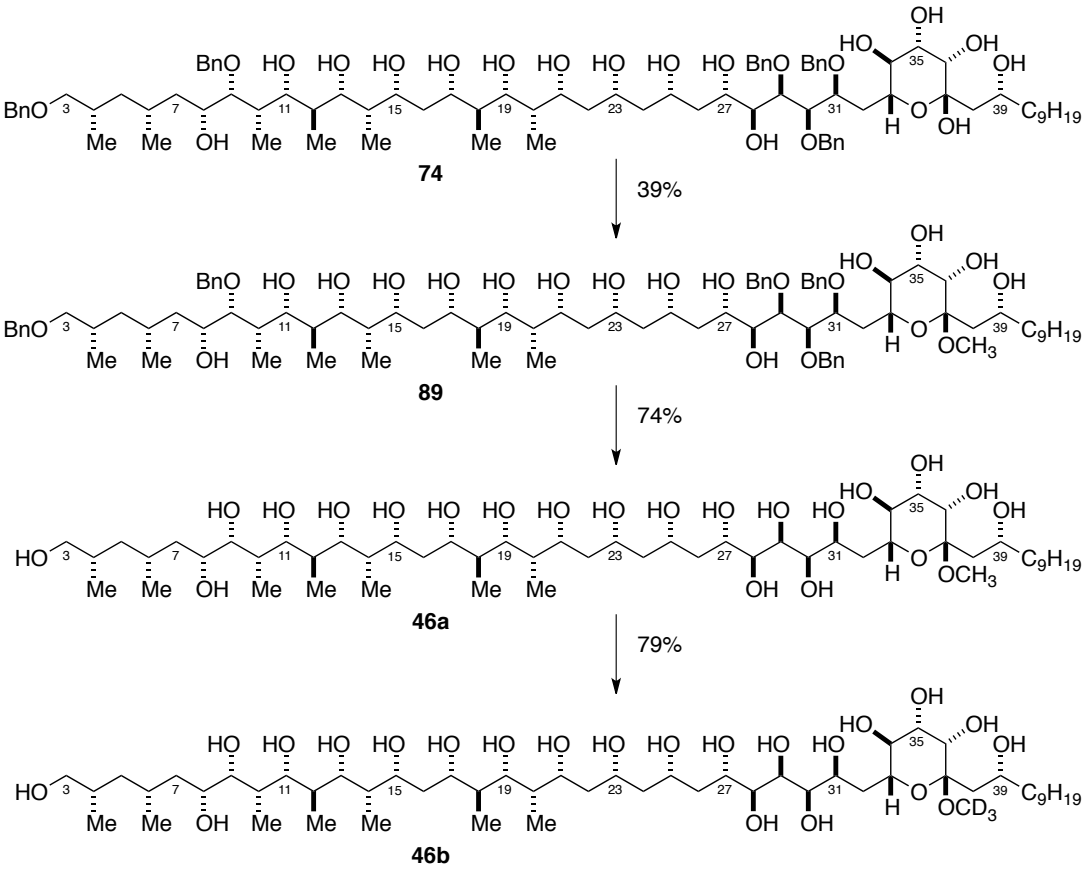
Synthesis of C27–C35 Aldehyde 67



Synthesis of C3–C48 Degradation Fragment 1



Synthesis of C3–C48 Degradation Fragments 46a and 46b



VIII. Experimental Section

General Information

Reactions in anhydrous solvents were carried out in glassware that was flame-dried or oven-dried. Unless noted, reactions were magnetically stirred and conducted under an atmosphere of nitrogen or argon. Air-sensitive reagents and solutions were transferred via syringe or cannula, and were introduced to reaction vessels through rubber septa. Reactions conducted below ambient temperature were cooled by external baths: dry ice/acetone for –78 °C to –5 °C, sodium chloride/ice water for –5 °C, and ice water for 0 °C. Reactions requiring more than 8 h at temperatures between –55 °C and 0 °C were chilled using an immersion cooler. Reactions conducted above ambient temperature were heated by a silicone oil bath. Analytical thin layer chromatography (TLC) was performed on EMD Reagent silica gel 60 F_{254} plates (210–270 μm layer thickness). Visualization was accomplished with ultraviolet light (254 nm) followed by heating after staining the plate with ceric ammonium molybdate or potassium permanganate solution. Extraction and chromatography solvents were reagent grade or HLPC grade, and were used without further purification. Brine solution refers to a saturated aqueous solution of sodium chloride. Product purification was performed by flash column chromatography[71] using Sorbent Technologies, Whatman, or Dynamic Adsorbents silica gel (32–63 μm, 230–400 mesh). Reversed-phase chromatography was performed using a Teledyne Isco CombiFlash® Rf 200 UV/Vis purification system and RediSep® Rf Gold C18 column (5.5 g, 20–40 μm).

Materials

Tetrahydrofuran, diethyl ether, toluene, and dichloromethane employed as reaction solvents were dried by passage through a column of activated alumina under an argon atmosphere.[72] Benzene, acetonitrile, and pentane employed as reaction solvent were distilled from calcium hydride prior to use. Methanol was distilled from magnesium methoxide prior to use. EMD DriSolv dimethyl sulfoxide and *N*,*N*-dimethylformamide were used without further purification. Triethylamine, Hünig's base, 2,6-lutidine, pyridine, dimethylethylamine, diisopropylamine, hexamethyldisilazane, and chlorotrimethylsilane were distilled from

(71) Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(72) Pangborn, A.B.; Giardello, M.A.; Grubbs, R.H.; Rosen, R.K.; Timmers, F.J. *Organometallics* **1996**, *15*, 1518–1520.

calcium hydride prior to use. Organolithium reagents (e.g. *n*-butyllithium, *t*-butyllithium, methyllithium) were purchased from commercial suppliers and were titrated prior to use using 2-butanol with 1,10-phenanthroline as indicator.[73] Grignard reagents were titrated using I_2 in THF. Dicyclohexylchloroborane was distilled under reduced pressure and stored under argon in a Schlenk flask. Trimethylsilyl, triethylsilyl, and *t*-butyldimethylsilyl trifluoromethanesulfonates, as well as boron trifluoride diethyl etherate were distilled from calcium hydride and stored under argon in Schlenk flasks. Benzyl bromide was purified by passage through a column of activated neutral alumina. Me(MeO)NH•HCl was dried azeotropically with benzene immediately prior to use. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was recrystallized from benzene and chloroform and stored under argon at –20 °C in a foil-wrapped vial. (*R*)-(–)- and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chlorides were purchased from the Sigma-Aldrich Chemical Company, and their absolute configurations were confirmed by optical rotation. Chloroform-*d* and benzene-d_6 were stored over 4Å molecular sieves.[74] Other reagents were purified, if necessary, according to the published methods.[75]

Analytical Information

Unless otherwise stated, all isolated and characterized compounds were >95% pure as judged by ^{1}H-NMR spectroscopic analysis. ^{1}H-NMR spectra were recorded at room temperature on an Agilent DD2 600 spectrometer (600 MHz), a Varian Inova 600 spectrometer (600 MHz), a Varian Inova 500 spectrometer (500 MHz), or a Mercury 400 spectrometer (400 MHz). ^{1}H-NMR data are reported in the following format: chemical shift (multiplicity, coupling constant(s), integration, proton assignment). Chemical shifts are reported in parts per million (ppm) from tetramethylsilane (δ scale) with the residual solvent resonance as internal standard (7.26 ppm for $CDCl_3$, 7.15 for C_6D_6, 3.30 for CD_3OD, and 7.55 pm for the middle peak of C_5D_5N). Multiplicity is abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. Proton assignments are referenced to the aflastatin A numbering system, and were made with the aid of 2D-COSY

(73) Watson, S.C.; Eastham, J.F. *J. Organomet. Chem.* **1967**, *9*, 165–168.

(74) (a) Burfield, D.R.; Gan, G.H.; Smithers, R.H. *J. Appl. Chem. & Biotechnol.* **1978**, *28*, 23–30. (b) Burfield, D.R.; Goh, E.H.; Ong, E.H.; Smithers, R.H. *Gazz. Chim. Ital.* **1983**, *113*, 841–843.

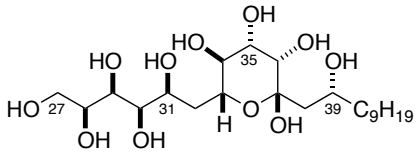
(75) Armarego, W.L.F.; Chai, C.L.L. *Purification of Laboratory Chemicals, 6th Ed.* Butterworth-Heinemann: Oxford, **2009**.

experiments. NOEs were measured by 2D-NOESY experiments or pulsed-field-gradient assisted 1D NOE experiments.

^{13}C-NMR spectra were recorded at room temperature on a Varian Inova 500 spectrometer (125 MHz), or a Mercury 400 spectrometer (100 MHz) with broadband proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane (δ scale) with the residual solvent resonance as internal standard (77.0 ppm for $CDCl_3$, 128.0 for C_6D_6, 49.0 for CD_3OD, and 135.5 pm for the middle peak of C_5D_5N). Carbon assignments are referenced to the aflastatin A numbering system, and were made with the aid of 2D-HSQC experiments.

Infrared spectra were recorded as thin films on NaCl plates using a Perkin Elmer 1600 series FT-IR spectrometer at a resolution of 4 cm^{-1}. Optical rotations were measured on a Jasco P-2000 series digital polarimeter with a sodium lamp, and are reported as $[\alpha]_D^{T\,(°C)}$ XX° (*c* (g/100 mL), solvent). High-resolution mass spectra were obtained on Agilent 6210 TOF or Bruker micrOTOF-Q II spectrometers at Harvard University's Small Molecule Mass Spectrometry Facility or Laukien-Purcell Instrumentation Center, respectively.

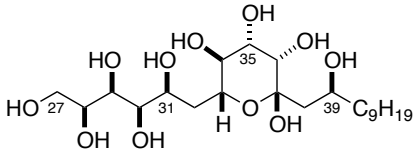
Spectroscopic Data for Model C27–C48 Lactols and Lactol Methyl Ethers



3a

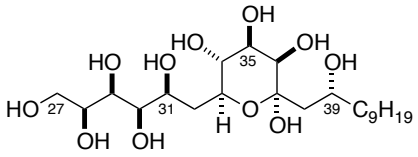
Aflastatin A Model C27–C48 Lactol (3a). White solid; $[\alpha]_D^{23}$ +12.8° (*c* = 0.50, CH_3OH); IR (neat) 3428 (br), 1638 cm^{-1}; ^{1}H-NMR (600 MHz, pyridine-d_5) δ 7.06 (br s, 1H, one of –O**H**), 6.80–5.80 (br s, 8H, eight of –O**H**), 5.00 (app dt, *J* = 7.0, 7.0, 2.0 Hz, 1H, C_{31}-**H**), 4.95 (br s, 1H, one of –O**H**), 4.89 (app dt, *J* = 10.0, 10.0, 3.0 Hz, 1H, C_{33}-**H**), 4.79 (dd, *J* = 9.5, 3.0 Hz, 1H, C_{35}-**H**), 4.76 (m, 1H, C_{39}-**H**), 4.72 (dd, *J* = 4.5, 3.5 Hz, 1H, C_{29}-**H**), 4.62–4.59 (m, 2H, C_{28}-**H** and C_{30}-**H**), 4.50 (d, *J* = 3.0 Hz, 1H, C_{36}-**H**), 4.41 (app t, *J* = 9.5, 9.5 Hz, 1H, C_{34}-**H**), 4.35–4.30 (m, 2H, C_{27}-**H$_2$**), 3.22 (ddd, *J* = 13.2, 8.0, 3.0 Hz, 1H, one of C_{32}-**H**), 2.75 (dd, *J* = 14.4, 1.8 Hz, 1H, one of C_{38}-**H**), 2.58 (ddd, *J* = 13.2, 10.0, 7.0 Hz, 1H, one of C_{32}-**H**), 2.15 (dd, *J* = 14.4, 10.9 Hz, 1H, one of C_{38}-**H**), 1.68–1.61 (m, 1H, one of C_{40}-**H**), 1.56–1.45 (m, 2H, one of C_{40}-**H** and one of C_{41}-**H**), 1.39–1.34 (m, 1H, one of C_{41}-**H**), 1.30–1.13 (m, 12H, $C_{42–47}$-**H$_2$**),

0.83 (t, J = 7.2 Hz, 3H, C_{48}-**H$_3$**); ^{13}C-NMR (125 MHz, pyridine-d_5) δ 100.2 (C37), 75.2 (C36), 73.8 (C34), 73.7 (C30), 73.5 (C29), 72.9 (C28 and C35), 71.6 (C31 and C33), 69.0 (C39), 64.6 (C27), 42.6 (C38), 39.6 (C40), 37.5 (C32), 32.1 (C46), 30.1 (C43 or C44), 29.9 (C43 or C44), 29.8 (C42), 29.6 (C45), 25.8 (C41), 22.9 (C47), 14.3 (C48); HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{44}NaO_{11}$ $[M+Na]^+$: 507.2776, found: 507.2788.



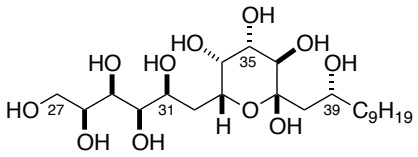
3b

***epi*-C39 Model C27–C48 Lactol (3b).** White solid; ^{1}H-NMR (600 MHz, pyridine-d_5) δ 6.84 (br s, 1H, one of –O**H**), 6.55 (br s, 2H, two of –O**H**), 6.44–6.22 (br m, 3H, three of –O**H**), 6.14 (br s, 1H, one of –O**H**), 5.98 (br s, 2H, two of –O**H**), 5.87 (br s, 1H, one of –O**H**), 4.88 (dd, J = 9.2, 2.8 Hz, 1H, C_{35}-**H**), 4.87 (app dt, J = 9.4, 9.4, 2.6 Hz, 1H, C_{33}-**H**), 4.83 (m, J = 7.3, 4.1 Hz, 1H, C_{31}-**H**), 4.59 (d, J = 2.8 Hz, 1H, C_{36}-**H**), 4.59 (m, 1H, C_{39}-**H**), 4.56 (dd, J = 3.8, 3.2 Hz, 1H, C_{29}-**H**), 4.54 (m, J = 3.5 Hz, 1H, C_{28}-**H**), 4.43 (m, 1H, C_{30}-**H**), 4.41 (app t, J = 9.1 Hz, 1H, C_{34}-**H**), 4.34–4.28 (m, J = 5.4, 4.5 Hz, 2H, C_{27}-**H$_2$**), 3.07 (ddd, J = 14.2, 4.1, 3.4 Hz, 1H, one of C_{32}-**H**), 2.62 (dd, J = 14.2 Hz, 1H, one of C_{38}-**H**), 2.53 (ddd, J = 14.2, 8.8, 7.9 Hz, 1H, one of C_{32}-**H**), 2.48 (dd, J = 14.2, 10.1 Hz, 1H, one of C_{38}-**H**), 1.77–1.73 (m, 1H, one of C_{40}-**H**), 1.62–1.56 (m, 2H, one of C_{40}-**H** and one of C_{41}-**H**), 1.47–1.42 (m, 1H, one of C_{41}-**H**), 1.27–1.11 (m, 12H, $C_{42–47}$-**H$_2$**), 0.82 (t, J = 7.2 Hz, 3H, C_{48}-**H$_3$**); ^{13}C-NMR (125 MHz, pyridine-d_5) δ 100.3 (C37), 74.8 (C30), 74.2 (C36), 74.1 (C28), 73.3 (C29), 73.1 (C35), 72.93 (C33), 72.87 (C34), 72.4 (C31), 67.6 (C39), 64.6 (C27), 45.3 (C38), 39.1 (C40), 37.3 (C32), 32.1 (C46), 30.04 (C43 or C44), 29.99 (C43 or C44), 29.8 (C42), 29.6 (C45), 26.2 (C41), 22.9 (C47), 14.3 (C48); ^{1}H-NMR (600 MHz, CD_3OD) δ 4.01 (ddd, J = 7.3, 5.5, 3.1 Hz, 1H, C_{31}-**H**), 3.94 (m, 1H, C_{39}-**H**), 3.85 (dd, J = 9.5, 3.4 Hz, 1H, C_{35}-**H**), 3.83 (ddd, J = 9.7, 9.5, 2.7 Hz, 1H, C_{33}-**H**), 3.79 (m, J = 3.4 Hz, 1H, C_{28}-**H**), 3.74 (dd, J = 4.7, 3.4 Hz, 1H, C_{29}-**H**), 3.68 (d, J = 3.4 Hz, 1H, C_{36}-**H**), 3.67–3.61 (m, 2H, C_{27}-**H$_2$**), 3.63 (dd, J = 4.7, 3.1 Hz, 1H, C_{30}-**H**), 3.42 (dd, J = 9.5, 9.4 Hz, 1H, C_{34}-**H**), 2.17 (ddd, J = 14.4, 5.5, 2.7 Hz, 1H, one of C_{32}-**H**), 1.88 (dd, J = 14.5, 1.9 Hz, 1H, one of C_{38}-**H**), 1.78 (dd, J = 14.6, 10.0 Hz, 1H, one of C_{38}-**H**), 1.73 (ddd, J = 14.4, 9.5, 7.3 Hz, 1H, one of C_{32}-**H**), 1.50–1.23 (m, 16H, $C_{40–47}$-**H$_2$**), 0.89 (t, J = 7.0 Hz, 3H, C_{48}-**H$_3$**).



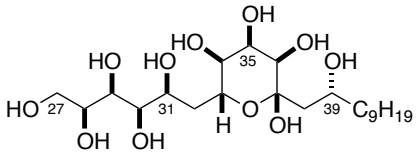
3c

***epi*-C33–C37 Model C27–C48 Lactol (3c).** White solid; ^{1}H-NMR (600 MHz, pyridine-d_5) δ 8.03 (br s, 1H, one of C_{37}–O**H**), 6.90 (br s, 1H, one of –O**H**), 6.51 (br s, 2H, two of –O**H**), 6.44–6.21 (br m, 3H, three of –O**H**), 6.12–6.01 (br m, 3H, three of –O**H**), 5.04 (ddd, *J* = 9.4, 9.2, 2.8 Hz, 1H, C_{33}-**H**), 4.91–4.90 (m, 2H, C_{30}-**H** and C_{31}-**H**), 4.64 (dd, *J* = 3.7, 3.2 Hz, 1H, C_{29}-**H**), 4.58 (d, *J* = 2.6 Hz, 1H, C_{36}-**H**), 4.58–4.54 (m, 2H, C_{28}-**H** and C_{39}-**H**), 4.38 (m, *J* = 9.4, 9.1 Hz, 1H, C_{34}-**H**), 4.35–4.26 (m, 3H, C_{27}-$\mathbf{H_2}$ and C_{35}-**H**), 3.11 (m, *J* = 2.6 Hz, 1H, one of C_{32}-**H**), 2.70 (dd, *J* = 13.2 Hz, 1H, one of C_{38}-**H**), 2.38 (dd, *J* = 14.2, 10.3 Hz, 1H, one of C_{38}-**H**), 2.32 (m, *J* = 11.8, 9.2 Hz, 1H, one of C_{32}-**H**), 1.76–1.72 (m, 1H, one of C_{40}-**H**), 1.62–1.56 (m, 2H, one of C_{40}-**H** and one of C_{41}-**H**), 1.48–1.41 (m, 1H, one of C_{41}-**H**), 1.26–1.05 (m, 12H, $C_{42–47}$-$\mathbf{H_2}$), 0.82 (t, *J* = 7.2 Hz, 3H, C_{48}-$\mathbf{H_3}$); ^{13}C-NMR (125 MHz, pyridine-d_5) δ 100.2 (C37), 76.1 (C35), 74.03 (C29), 73.99 (C36), 73.3 (C30), 73.2 (C28), 73.0 (C34), 71.1 (C33), 69.9 (C31), 67.9 (C39), 64.6 (C27), 44.8 (C38), 39.0 (C40), 38.5 (C32), 32.1 (C46), 30.04 (C43 or C44), 29.99 (C43 or C44), 29.8 (C42), 29.6 (C45), 26.2 (C41), 22.9 (C47), 14.3 (C48); ^{1}H-NMR (600 MHz, CD_3OD) δ 3.97 (ddd, *J* = 10.3, 3.5, 3.1 Hz, 1H, C_{31}-**H**), 3.94 (m, 1H, C_{39}-**H**), 3.88 (dd, *J* = 9.5, 3.4 Hz, 1H, C_{35}-**H**), 3.87 (ddd, *J* = 9.7, 9.7, 2.8 Hz, 1H, C_{33}-**H**), 3.78 (ddd, *J* = 6.2, 5.0, 3.5 Hz, 1H, C_{28}-**H**), 3.73 (dd, *J* = 4.5, 3.5 Hz, 1H, C_{29}-**H**), 3.70 (d, *J* = 3.4 Hz, 1H, C_{36}-**H**), 3.66 (d, *J* = 11.1, 5.0 Hz, 1H, one of C_{27}-**H**), 3.63 (d, *J* = 11.1, 6.2 Hz, 1H, one of C_{27}-**H**), 3.57 (dd, *J* = 4.2, 4.0 Hz, 1H, C_{30}-**H**), 3.40 (dd, *J* = 9.7, 9.5 Hz, 1H, C_{34}-**H**), 2.15 (ddd, *J* = 14.4, 10.0, 2.6 Hz, 1H, one of C_{32}-**H**), 1.93 (dd, *J* = 14.6, 1.9 Hz, 1H, one of C_{38}-**H**), 1.75 (dd, *J* = 14.6, 10.0 Hz, 1H, one of C_{38}-**H**), 1.61 (ddd, *J* = 14.4, 9.8, 2.9 Hz, 1H, one of C_{32}-**H**), 1.50–1.38 (m, 2H, C_{40}-$\mathbf{H_2}$), 1.37–1.23 (m, 14H, $C_{41–47}$-$\mathbf{H_2}$), 0.89 (t, *J* = 7.1 Hz, 3H, C_{48}-$\mathbf{H_3}$).



3d

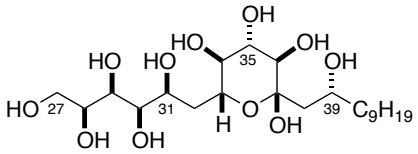
***epi*-C34,C36 Model C27–C48 Lactol (3d).** White solid; ^{1}H-NMR (600 MHz, pyridine-d_5) δ 7.46 (br s, 1H, one of –O**H**), 6.96 (br s, 1H, one of –O**H**), 6.54 (br s, 1H, one of –O**H**), 6.38–6.28 (br m, 2H, two of –O**H**), 6.25–6.12 (br m, 4H, four of –O**H**), 5.07 (ddd, *J* = 7.5, 6.9 Hz, 1H, C_{33}-**H**), 4.85 (m, 1H, C_{31}-**H**), 4.69 (m, 1H, C_{39}-**H**), 4.68 (dd, *J* = 3.4, 3.2 Hz, 1H, C_{30}-**H**), 4.59 (m, *J* = 3.5 Hz, 1H, C_{28}-**H**), 4.56 (dd, *J* = 10.1, 3.1 Hz, 1H, C_{35}-**H**), 4.48 (m, 1H, C_{29}-**H**), 4.44 (m, 1H, C_{34}-**H**), 4.38 (d, *J* = 9.7 Hz, 1H, C_{36}-**H**), 4.35–4.29 (m, 2H, C_{27}-$\mathbf{H_2}$), 2.96 (ddd, *J* = 13.5, 8.1, 7.9 Hz, 1H, one of C_{32}-**H**), 2.69 (ddd, *J* = 13.4, 6.7, 5.9 Hz, 1H, one of C_{32}-**H**), 2.64 (dd, *J* = 14.1, 11.3 Hz, 1H, one of C_{38}-**H**), 2.04 (dd, *J* = 13.9 Hz, 1H, one of C_{38}-**H**), 1.64–1.59 (m, 1H, one of C_{40}-**H**), 1.51–1.42 (m, 2H, one of C_{40}-**H** and one of C_{41}-**H**), 1.38–1.31 (m, 1H, one of C_{41}-**H**), 1.26–1.11 (m, 12H, $C_{42–47}$-$\mathbf{H_2}$), 0.82 (t, *J* = 7.1 Hz, 3H, C_{48}-$\mathbf{H_3}$); ^{13}C-NMR (125 MHz, pyridine-d_5) δ 100.1 (C37), 74.3 (C36), 74.2 (C29), 73.9 (C28), 73.5 (C30), 72.5 (C35), 72.1 (C34), 70.6 (C31), 69.3 (C33), 68.2 (C39), 64.5 (C27), 43.8 (C38), 39.2 (C40), 35.7 (C32), 32.0 (C46), 30.0 (C43 or C44), 29.9 (C43 or C44), 29.8 (C42), 29.5 (C45), 25.8 (C41), 22.9 (C47), 14.2 (C48).



3e

***epi*-C35,C36 Model C27–C48 Lactol (3e).** White solid; ^{1}H-NMR (600 MHz, pyridine-d_5) δ 7.52 (br s, 1H, one of –O**H**), 7.32 (br s, 1H, one of –O**H**), 7.07 (br s, 1H, one of –O**H**), 6.47–6.37 (br m, 4H, four of –O**H**), 6.09–6.03 (br m, 3H, three of –O**H**), 4.96–4.90 (m, *J* = 9.8, 3.4 Hz, 2H, C_{31}-**H** and C_{33}-**H**), 4.74–4.66 (m, 2H, C_{29}-**H** and C_{35}-**H**), 4.62–4.55 (m, 2H, C_{28}-**H** and C_{39}-**H**), 4.55–4.49 (m, 1H, C_{30}-**H**), 4.37–4.28 (m, 2H, C_{27}-$\mathbf{H_2}$), 3.92–3.89 (m, 1H, C_{36}-**H**), 3.86 (m, *J* = 8.6 Hz, 1H, C_{34}-**H**), 3.09 (ddd, *J* = 14.2, 5.9, 3.4 Hz, 1H, one of C_{32}-**H**), 2.51 (ddd, *J* = 14.1, 9.8, 7.1 Hz, 1H, one of C_{32}-**H**), 2.45 (dd, *J* = 14.3, 10.5 Hz, 1H, one of C_{38}-**H**), 2.16 (dd, *J* = 14.2 Hz, 1H, one of C_{38}-**H**), 1.69–1.64 (m, 1H, one of C_{40}-**H**), 1.60–1.47 (m, 2H, one of C_{40}-**H** and one of C_{41}-**H**), 1.46–1.39 (m, 1H, one of C_{41}-**H**), 1.26–1.11 (m, 12H, $C_{42–47}$-$\mathbf{H_2}$), 0.82 (t, *J* = 7.2 Hz, 3H, C_{48}-$\mathbf{H_3}$); ^{13}C-NMR (125 MHz, pyridine-d_5) δ 100.8 (C37), 74.4 (C35), 74.00 (C30), 73.95 (C28), 73.5 (C29), 73.1 (C34), 71.8 (C36), 71.6 (C31), 67.8 (C39), 67.3 (C33), 64.6 (C27), 45.7 (C38), 38.9 (C40), 37.2 (C32), 32.1 (C46), 30.1 (C43 or C44), 29.9 (C43 or C44), 29.8 (C42), 29.6 (C45), 26.0 (C41), 22.9 (C47), 14.3 (C48); ^{1}H-NMR (600

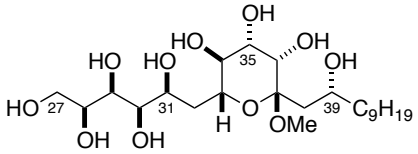
MHz, CD_3OD) δ 4.07 (ddd, *J* = 6.7, 6.6, 2.7 Hz, 1H, C_{31}-**H**), 4.03 (ddd, *J* = 9.8, 9.8, 3.1 Hz, 1H, C_{33}-**H**), 4.03–3.98 (m, 1H, C_{39}-**H**), 4.01 (dd, *J* = 3.1, 2.9 Hz, 1H, C_{35}-**H**), 3.79 (ddd, *J* = 6.3, 5.1, 3.1 Hz, 1H, C_{28}-**H**), 3.78–3.75 (m, 1H, C_{30}-**H**), 3.68 (dd, *J* = 5.0, 2.7 Hz, 1H, C_{29}-**H**), 3.67–3.62 (m, 2H, C_{27}-$\mathbf{H_2}$), 3.34 (d, *J* = 3.1 Hz, 1H, C_{36}-**H**), 3.28 (dd, *J* = 9.8, 2.9 Hz, 1H, C_{34}-**H**), 2.21 (ddd, *J* = 14.1, 6.7, 3.1 Hz, 1H, one of C_{32}-**H**), 1.86 (dd, *J* = 14.6, 10.4 Hz, 1H, one of C_{38}-**H**), 1.70 (ddd, *J* = 14.2, 9.7, 6.6 Hz, 1H, one of C_{32}-**H**), 1.67 (dd, *J* = 14.5, 1.8 Hz, 1H, one of C_{38}-**H**), 1.45–1.22 (m, 16H, $C_{40–47}$-$\mathbf{H_2}$), 0.90 (t, *J* = 7.0 Hz, 3H, C_{48}-$\mathbf{H_3}$).



3f

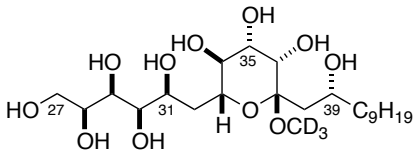
***epi*-C36 Model C27–C48 Lactol (3f).** White solid; ^{1}H-NMR (600 MHz, pyridine-d_5) δ 7.53 (br s, 1H, one of –O**H**), 6.99–6.96 (br m, *J* = 4.2, 4.0 Hz, 2H, two of –O**H**), 6.84 (br s, 1H, one of –O**H**), 6.58 (br s, 1H, one of –O**H**), 6.53–6.49 (br s, 2H, two of –O**H**), 6.10–6.05 (br m, 2H, two of –O**H**), 5.98 (br d, *J* = 4.0 Hz, 1H, one of –O**H**), 4.95 (m, 1H, C_{31}-**H**), 4.90 (ddd, *J* = 9.8, 9.7, 3.1 Hz, 1H, C_{33}-**H**), 4.72–4.66 (m, 2H, C_{29}-**H** and C_{39}-**H**), 4.61–4.56 (m, *J* = 9.8, 7.6 Hz, 3H, C_{28}-**H**, C_{30}-**H** and C_{35}-**H**), 4.34–4.28 (m, 2H, C_{27}-$\mathbf{H_2}$), 3.94 (ddd, *J* = 9.8, 9.2, 3.6 Hz, 1H, C_{34}-**H**), 3.91 (dd, *J* = 8.2, 7.8 Hz, 1H, C_{36}-**H**), 3.21 (ddd, *J* = 13.8, 7.0, 3.4 Hz, 1H, one of C_{32}-**H**), 2.67 (dd, *J* = 14.2, 11.1 Hz, 1H, one of C_{38}-**H**), 2.51 (ddd, *J* = 13.8, 10.0, 6.6 Hz, 1H, one of C_{32}-**H**), 2.06 (dd, *J* = 12.9 Hz, 1H, one of C_{38}-**H**), 1.66–1.60 (m, 1H, one of C_{40}-**H**), 1.54–1.46 (m, 2H, one of C_{40}-**H** and one of C_{41}-**H**), 1.42–1.34 (m, 1H, one of C_{41}-**H**), 1.26–1.11 (m, 12H, $C_{42–47}$-$\mathbf{H_2}$), 0.82 (t, *J* = 7.2 Hz, 3H, C_{48}-$\mathbf{H_3}$); ^{13}C-NMR (125 MHz, pyridine-d_5) δ 99.8 (C37), 77.8 (C36), 77.1 (C34), 75.8 (C29), 73.8 (C30), 73.6 (C28), 73.1 (C35), 71.5 (C31), 70.7 (C33), 68.3 (C39), 64.5 (C27), 43.8 (C38), 39.2 (C40), 37.6 (C32), 32.0 (C46), 30.1 (C43 or C44), 29.9 (C43 or C44), 29.8 (C42), 29.5 (C45), 25.8 (C41), 22.9 (C47), 14.2 (C48); ^{1}H-NMR (600 MHz, CD_3OD) δ 4.08–4.02 (m, *J* = 8.3, 6.3, 2.3 Hz, 2H, C_{31}-**H** and C_{39}-**H**), 3.89 (ddd, *J* = 10.0, 9.8, 2.9 Hz, 1H, C_{33}-**H**), 3.79–3.76 (m, *J* = 5.1, 3.1 Hz, 2H, C_{28}-**H** and C_{29}-**H**), 3.68–3.62 (m, *J* = 8.2, 6.1 Hz, 2H, C_{27}-$\mathbf{H_2}$), 3.67 (dd, *J* = 5.1, 2.5 Hz, 1H, C_{30}-**H**), 3.58 (app t, *J* = 9.2 Hz, 1H, C_{35}-**H**), 3.10 (d, *J* = 9.4 Hz, 1H, C_{36}-**H**), 3.09 (app t, *J* = 9.4 Hz, 1H, C_{34}-**H**), 2.23 (ddd, *J* = 13.9, 7.5, 2.9 Hz, 1H, one of C_{32}-**H**), 1.93 (dd, *J* = 14.5, 10.8 Hz, 1H, one of C_{38}-**H**), 1.66 (ddd, *J* = 13.9, 10.1, 6.3 Hz, 1H, one of C_{32}-**H**), 1.62 (dd, *J* =

14.4, 1.9 Hz, 1H, one of C_{38}-**H**), 1.48–1.24 (m, 16H, $C_{40–47}$-$\mathbf{H_2}$), 0.89 (t, *J* = 7.0 Hz, 3H, C_{48}-$\mathbf{H_3}$).



51a

Aflastatin A Model C27–C48 Lactol Methyl Ether (51a). White solid; $[\alpha]_D^{24}$ +19.8° (*c* = 0.30, CH_3OH); IR (neat) 3362 (br), 2926, 2855, 1456, 1377, 1206, 1102, 1063 cm^{-1}; ^{1}H-NMR (600 MHz, pyridine-d_5) δ 6.87 (br s, 1H, one of –O**H**), 6.48 (br s, 2H, two of –O**H**), 6.42–5.99 (br m, 6H, six of –O**H**), 4.94 (m, *J* = 6.2, 2.9 Hz, 1H, C_{31}-**H**), 4.70–4.66 (m, *J* = 3.6 Hz, 2H, C_{29}-**H** and C_{36}-**H**), 4.65 (ddd, *J* = 5.6, 5.1, 3.5 Hz, 1H, C_{28}-**H**), 4.58 (dd, *J* = 9.3, 3.6 Hz, 1H, C_{35}-**H**), 4.52 (dd, *J* = 3.5, 3.4 Hz, 1H, C_{30}-**H**), 4.38–4.32 (m, *J* = 10.8, 4.5 Hz, 2H, C_{27}-$\mathbf{H_2}$), 4.33 (app t, *J* = 9.1 Hz, 1H, C_{34}-**H**), 4.26 (app dt, *J* = 9.2, 9.2, 2.8 Hz, 1H, C_{33}-**H**), 4.22–4.17 (m, *J* = 7.3, 5.0 Hz, 1H, C_{39}-**H**), 3.37 (s, 3H, C_{56}-$\mathbf{H_3}$), 3.20 (ddd, *J* = 14.2, 6.4, 2.7 Hz, 1H, one of C_{32}-**H**), 2.50 (ddd, *J* = 14.6, 8.9, 5.9 Hz, 1H, one of C_{32}-**H**), 2.46 (dd, *J* = 15.1, 9.3 Hz, 1H, one of C_{38}-**H**), 2.23 (app d, *J* = 14.9 Hz, 1H, one of C_{38}-**H**), 1.71–1.64 (m, 1H, one of C_{40}-**H**), 1.63–1.53 (m, 2H, one of C_{40}-**H** and one of C_{41}-**H**), 1.52–1.43 (m, 1H, one of C_{41}-**H**), 1.32–1.14 (m, 12H, $C_{42–47}$-$\mathbf{H_2}$), 0.82 (t, *J* = 7.0 Hz, 3H, C_{48}-$\mathbf{H_3}$); ^{13}C-NMR (125 MHz, pyridine-d_5) δ 103.3 (C37), 74.3 (C30), 73.9 (C28), 73.6 (C29), 73.1 (C36), 72.8 (C33), 72.7 (C35), 72.4 (C34), 71.3 (C31), 67.0 (C39), 64.7 (C27), 47.9 (C56), 39.42 (C38 or C40), 39.36 (C38 or C40), 37.5 (C32), 32.1 (C46), 30.03 (C43 or C44), 29.97 (C43 or C44), 29.8 (C42), 29.5 (C45), 26.0 (C41), 22.9 (C47), 14.2 (C48); HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{46}NaO_{11}$ $[M+Na]^+$: 521.2932, found: 521.2926.

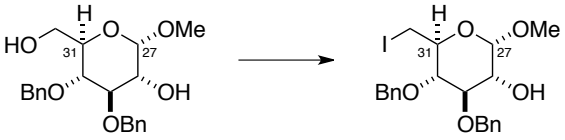


51b

Aflastatin A Model C27–C48 Lactol Trideuteriomethyl Ether (51b). White solid; $[\alpha]_D^{24}$ +22.9° (*c* = 0.38, CH_3OH); IR (neat) 3365 (br), 2926, 2855, 2072, 1456, 1418, 1260, 1207, 1114, 1062 cm^{-1}; ^{1}H-NMR (600 MHz, pyridine-d_5) δ 6.13 (br s, 9H, nine of –O**H**), 4.94 (app

dt, J = 6.2, 6.2, 3.2 Hz, 1H, C_{31}-**H**), 4.70–4.66 (m, J = 3.6 Hz, 2H, C_{29}-**H** and C_{36}-**H**), 4.65 (ddd, J = 5.7, 5.3 Hz, 1H, C_{28}-**H**), 4.58 (dd, J = 9.2, 3.7 Hz, 1H, C_{35}-**H**), 4.52 (dd, J = 3.8, 3.4 Hz, 1H, C_{30}-**H**), 4.38–4.32 (m, J = 10.8, 5.3 Hz, 2H, C_{27}-$\mathbf{H_2}$), 4.33 (app t, J = 9.5 Hz, 1H, C_{34}-**H**), 4.26 (app dt, J = 9.2, 9.2, 2.6 Hz, 1H, C_{33}-**H**), 4.21–4.17 (m, J = 5.9 Hz, 1H, C_{39}-**H**), 3.20 (ddd, J = 14.1, 6.4, 2.8 Hz, 1H, one of C_{32}-**H**), 2.50 (ddd, J = 14.6, 8.7, 5.9 Hz, 1H, one of C_{32}-**H**), 2.46 (dd, J = 15.3, 9.3 Hz, 1H, one of C_{38}-**H**), 2.22 (app d, J = 14.9 Hz, 1H, one of C_{38}-**H**), 1.71–1.64 (m, 1H, one of C_{40}-**H**), 1.63–1.53 (m, 2H, one of C_{40}-**H** and one of C_{41}-**H**), 1.52–1.43 (m, 1H, one of C_{41}-**H**), 1.32–1.14 (m, 12H, $C_{42–47}$-$\mathbf{H_2}$), 0.82 (t, J = 7.0 Hz, 3H, C_{48}-$\mathbf{H_3}$); ^{13}C-NMR (125 MHz, pyridine-d_5) δ 103.3 (C37), 74.3 (C30), 73.9 (C28), 73.6 (C29), 73.1 (C36), 72.8 (C33), 72.6 (C35), 72.4 (C34), 71.3 (C31), 66.9 (C39), 64.6 (C27), 39.42 (C38 or C40), 39.36 (C38 or C40), 37.5 (C32), 32.1 (C46), 30.03 (C43 or C44), 29.97 (C43 or C44), 29.8 (C42), 29.5 (C45), 26.0 (C41), 22.9 (C47), 14.2 (C48); HRMS (ESI-TOF) m/z calcd for $C_{23}H_{43}D_3NaO_{11}$ $[M+Na]^+$: 524.3121, found: 524.3100.

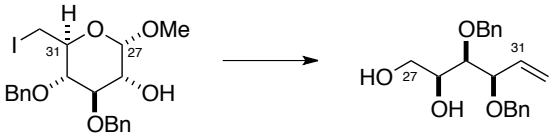
Synthesis of the C27–C35 Aldehyde



62 **78**

(2*S*,3*R*,4*R*,5*S*,6*S*)-4,5-Bis(benzyloxy)-6-(iodomethyl)-2-methoxytetrahydro-2*H*-pyran-3-ol (78). To a solution of diol **62** (9.8 g, 26 mmol, 1.0 equiv), imidazole (5.4 g, 79 mmol, 3.0 equiv), and triphenylphosphine (10.7 g, 40.7 mmol, 1.55 equiv) in 2:1 PhMe/MeCN (131 mL, 0.2 M wrt **62**) at rt was added iodine (10 g, 39 mmol, 1.5 equiv) in three portions. The reaction mixture was stirred at rt for 3 h, quenched with brine (100 mL), and then diluted with H_2O (10 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 5:1 → 4:1 → 3:1 hexanes/EtOAc) afforded iodide **78** (12.3 g, 97% yield) as a white solid. $[\alpha]_D^{25}$ +95.4° (c = 2.3, CH_2Cl_2); IR (neat) 3424 (br), 3029, 2924, 1497, 1453, 1399, 1361, 1325, 1214, 1192, 1140, 1087, 1046, 733, 696 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.39–7.30 (m, 10H, Ar**H**), 4.95 (d, J = 11.0 Hz, 1H, one of –OC$\mathbf{H_2}$Ph), 4.94 (d, J = 11.1 Hz, 1H, one of –OC$\mathbf{H_2}$Ph), 4.84

(d, J = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.78 (d, J = 3.8 Hz, 1H, C_{27}-**H**), 4.72 (d, J = 11.0 Hz, 1H, one of –OC**H**$_2$Ph), 3.80 (dd, J = 9.2, 8.9 Hz, 1H, C_{29}-**H**), 3.71 (ddd, J = 8.8, 8.6, 3.8 Hz, 1H, C_{28}-**H**), 3.51 (dd, J = 10.5, 2.6 Hz, 1H, one of C_{32}-**H**), 3.48 (ddd, J = 9.1, 6.4, 2.6 Hz, 1H, C_{31}-**H**), 3.48 (s, 3H, –OC**H**$_3$), 3.36 (dd, J = 9.2, 8.9 Hz, 1H, C_{30}-**H**), 3.32 (dd, J = 10.5, 6.3 Hz, 1H, one of C_{32}-**H**), 2.16 (d, J = 8.6 Hz, 1H, C_{28}-O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.4, 137.9, 128.5, 128.5, 127.9, 127.9, 127.8, 99.3, 82.8, 81.2, 75.4, 75.3, 73.1, 69.7, 55.5, 7.3; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{25}INaO_5$ $[M+Na]^+$: 507.06389, found: 507.06416.

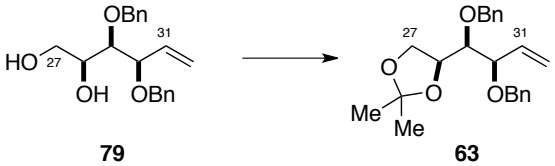


78 **79**

((2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)hex-5-ene-1,2-diol (79). To a solution of iodide **78** (1.1 g, 2.2 mmol, 1.0 equiv) in 4:1 THF/H_2O (22 mL, 0.1 M wrt **78**) at rt was added preactivated zinc dust[76] (1.4 g, 22 mmol, 10 equiv). The reaction mixture was sonicated at 40–45 °C for 4 h, then cooled to 0 °C and charged with sodium borohydride (0.17 g, 4.4 mmol, 2.0 equiv) in three portions. The resulting suspension was stirred at 0 °C for 2 h, slowly quenched with 1 M $NaHSO_4$ (15 mL), diluted with Et_2O (15 mL), warmed to rt, and filtered through Celite®. The filter cake was rinsed with Et_2O (3 x 10 mL) and sat. aq NH_4Cl (3 x 10 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 2:1 → 3:2 → 1:1 hexanes/EtOAc) afforded diol **79** (0.56 g, 78% yield) as a clear, colorless oil. $[\alpha]_D^{25}$ +7.6° (c = 0.66, CH_2Cl_2); IR (neat) 3419 (br), 3064, 3031, 2934, 2877, 1497, 1455, 1403, 1351, 1209, 1066, 1028, 998, 931, 870, 736, 699 cm^{-1}; ^{1}H-NMR (600 MHz, C_6D_6) δ 7.27 (m, 2H, two of Ar**H**), 7.22 (m, 2H, two of Ar**H**), 7.17–7.12 (m, 4H, four of Ar**H**), 7.08 (m, 2H, two of Ar**H**), 5.78 (ddd, J = 17.4, 10.4, 7.3 Hz, 1H, C_{31}-**H**), 5.24 (d, J = 17.4 Hz, 1H, one of C_{32}-**H**), 5.11 (d, J = 10.4 Hz, 1H, one of C_{32}-**H**), 4.75 (d, J = 11.3 Hz, 1H, one of –OC**H**$_2$Ph), 4.49 (d, J = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.43 (d, J = 11.3 Hz, 1H, one of –OC**H**$_2$Ph), 4.22 (d, J = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.11 (dd, J = 7.3, 6.4 Hz, 1H, C_{30}-**H**), 3.76 (dddd, J = 7.6, 5.4, 5.4, 3.4 Hz, 1H, C_{28}-**H**), 3.55–3.47 (m, J = 11.1,

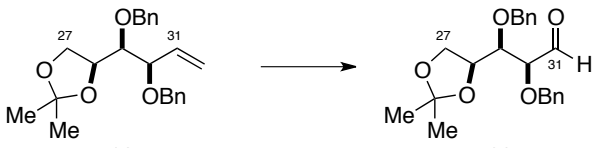
(76) Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444–8452.

7.8, 5.4, 4.8 Hz, 2H, C_{27}-**H**$_2$), 3.45 (dd, *J* = 6.4, 3.4 Hz, 1H, C_{29}-**H**), 2.41 (d, *J* = 7.6 Hz, 1H, C_{28}-O**H**), 1.86 (dd, *J* = 7.8, 4.8 Hz, 1H, C_{27}-O**H**); ^{13}C-NMR (125 MHz, C_6D_6) δ 138.9, 138.9, 135.6, 128.6, 128.6, 128.3, 128.1, 127.9, 127.7, 118.9, 82.1, 81.6, 74.8, 71.4, 70.9, 64.3; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{24}NaO_4$ [M+Na]$^+$: 351.15668, found: 351.15697.



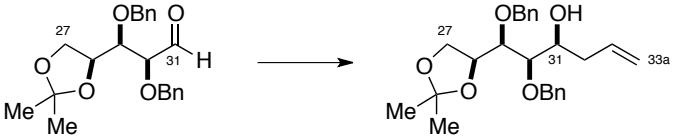
79 **63**

(*S*)-4-((1*S*,2*R*)-1,2-Bis(benzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane (63). To a solution of diol **79** (2.7 g, 8.1 mmol, 1.0 equiv) in 2:1 acetone/2,2-dimethoxypropane (81 mL, 0.1 M wrt **79**) at rt was added PPTS (10 mg, 41 μmol, 0.005 equiv). The reaction mixture was stirred at rt for 10 h, quenched with a small spatula tip full of $NaHCO_3$ (s), stirred vigorously for an additional 15 min, and filtered through Celite®. The filter cake was rinsed with EtOAc (40 mL total), and the filtrate concentrated. Column chromatography (gradient elution, 4% → 6% → 8% EtOAc in hexanes) afforded acetonide **63** (2.7 g, 90% yield) as a clear, colorless oil. $[\alpha]_D^{24}$ –25.3° (*c* = 2.1, CH_2Cl_2); IR (neat) 3065, 3031, 2985, 2873, 1497, 1455, 1380, 1252, 1213, 1070, 1001, 930, 861, 736, 698 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.35–7.26 (m, 10H, Ar**H**), 5.90 (ddd, *J* = 17.4, 10.4, 7.0 Hz, 1H, C_{31}-**H**), 5.33 (d, *J* = 17.4 Hz, 1H, one of C_{32}-**H**), 5.31 (d, *J* = 10.4 Hz, 1H, one of C_{32}-**H**), 4.79 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.76 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.60 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.34 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.27 (ddd, *J* = 7.8, 6.4, 6.4 Hz, 1H, C_{28}-**H**), 3.93 (dd, *J* = 6.7, 5.1 Hz, 1H, C_{30}-**H**), 3.82 (dd, *J* = 8.2, 6.3 Hz, 1H, one of C_{27}-**H**), 3.65 (dd, *J* = 8.1, 8.1, 1H, one of C_{27}-**H**), 3.45 (dd, *J* = 6.6, 4.8 Hz, 1H, C_{29}-**H**), 1.40 (s, 3H, one of C**H**$_3$), 1.35 (s, 3H, one of C**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.6, 138.1, 134.9, 128.3, 128.2, 128.2, 128.1, 128.0, 127.8, 127.6, 127.4, 118.4, 108.7, 81.3, 80.5, 76.8, 74.0, 70.6, 65.9, 26.6, 25.7; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{28}NaO_4$ [M+Na]$^+$: 391.18798, found: 391.18848.



63 **80**

(2*S*,3*R*)-2,3-Bis(benzyloxy)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)propanal (80). To a solution of alkene **63** (0.55 g, 1.5 mmol, 1.0 equiv) in 1:1 CH_2Cl_2/MeOH (30 mL, 0.05 M wrt **63**) at –78 °C was added pyridine (1.2 mL, 15 mmol, 10 equiv). The reaction mixture was bubbled with ozone until it turned blue, purged with oxygen until the color faded, quenched dropwise with a solution of triphenylphosphine (0.47 g, 1.8 mmol, 1.2 equiv) in 1:1 CH_2Cl_2/MeOH (7.4 mL, 0.24 M wrt PPh_3), slowly warmed to rt o/n (16 h total stir time), and then diluted with 1 M aq $NaHSO_4$ (40 mL) and brine (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. A sufficient quantity of crude aldehyde **80** was purified by column chromatography (4:1 hexanes/EtOAc) for characterization. $[\alpha]_D^{24}$ –30.9° (*c* = 6.4, CH_2Cl_2); IR (neat) 3032, 2987, 2936, 2874, 1732 (s), 1498, 1455, 1371, 1255, 1211, 1152 1077, 850, 739, 699 cm^{-1}; ^{1}H-NMR (600 MHz, C_6D_6) δ 9.70 (d, *J* = 1.2 Hz, 1H, C_{31}-**H**), 7.25 (m, 2H, two of Ar**H**), 7.17–7.05 (m, 8H, eight of Ar**H**), 4.56 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.52 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.50 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.40 (ddd, *J* = 7.2, 6.7, 5.4 Hz, 1H, C_{28}-**H**), 4.15 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 3.69 (dd, *J* = 4.5, 1.3 Hz, 1H, C_{30}-**H**), 3.69 (dd, *J* = 8.2, 6.6 Hz, 1H, one of C_{27}-**H**), 3.61 (dd, *J* = 8.3, 7.2 Hz, 1H, one of C_{27}-**H**), 3.45 (dd, *J* = 5.4, 4.5 Hz, 1H, C_{29}-**H**), 1.38 (s, 3H, one of C**H**$_3$), 1.24 (s, 3H, one of C**H**$_3$); ^{13}C-NMR (125 MHz, C_6D_6) δ 201.0, 138.5, 137.7, 128.6, 128.5, 128.3, 128.2, 128.2, 127.9, 127.8, 109.7, 83.0, 79.9, 76.3, 73.7, 73.1, 65.8, 26.5, 25.7; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{26}NaO_5$ $[M+Na]^+$: 393.16725, found: 393.16666.

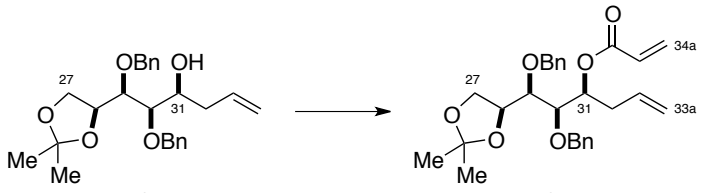


80 **64**

(1*R*,2*R*,3*S*)-1,2-Bis(benzyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)hex-5-en-3-ol (64). To a solution of crude aldehyde **80** (theoretical 0.55 g, 1.5 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL, 0.05 M wrt **80**) at 0 °C was added freshly prepared[77] $MgBr_2$•OEt_2 (1.5 g, 6.0 mmol, 4.0 equiv). The resulting suspension was stirred at 0 °C for 5 min, cooled to –78 °C, and then

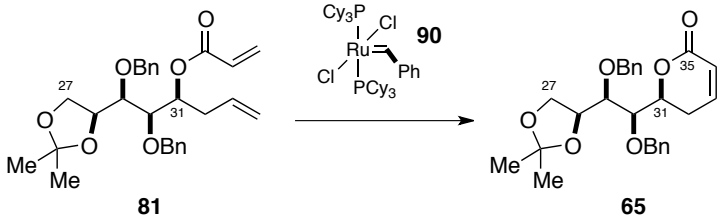
(77) Peterson, S. *Studies Toward the Synthesis of Amphidinol 3*. Ph.D. Thesis, Harvard University, **2006**.

charged dropwise with a freshly prepared[78] solution of allylmagnesium bromide in Et_2O (5.3 mL, 0.42 M, 2.2 mmol, 1.5 equiv). The reaction mixture was stirred at –78 °C for 2.5 h, slowly warmed to –40 °C over 30 min, then briefly warmed to 0 °C and quenched with sat. aq NH_4Cl (30 mL). The biphasic mixture was diluted with H_2O (5 mL) and CH_2Cl_2 (30 mL) and warmed to rt. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was analyzed by ^{1}H-NMR spectroscopy to assess reaction diastereoselectivity (d.r. = 89:11). Column chromatography (gradient elution, 16% → 18% → 20% EtOAc in hexanes) afforded homoallylic carbinol **64** (0.35 g, 56% yield, two steps) as a clear, colorless oil. $[\alpha]_D^{25}$ –18.9° (*c* = 1.4, CH_2Cl_2); IR (neat) 3477 (br), 3065, 3031, 2984, 2935, 1641, 1497, 1454, 1371, 1249, 1211, 1068, 916, 858, 736, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.36–7.29 (m, 8H, eight of Ar**H**), 7.27 (m, 2H, two of Ar**H**), 5.77 (dddd, *J* = 17.1, 10.3, 7.0, 7.0 Hz, 1H, C_{33}-**H**), 5.07 (d, *J* = 10.3 Hz, 1H, one of C_{33a}-**H**), 5.03 (dd, *J* = 17.1, 1.5 Hz, 1H, one of C_{33a}-**H**), 4.68 (d, *J* = 12.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.66 (d, *J* = 12.3 Hz, 1H, one of –OC**H**$_2$Ph), 4.64 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.52 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.44 (ddd, *J* = 6.7, 6.7, 5.6 Hz, 1H, C_{28}-**H**), 3.95 (dd, *J* = 8.1, 6.7 Hz, 1H, one of C_{27}-**H**), 3.90 (dddd, *J* = 7.6, 7.0, 5.4, 2.2 Hz, 1H, C_{31}-**H**), 3.78 (dd, *J* = 7.8, 7.8 Hz, 1H, one of C_{27}-**H**), 3.55 (dd, *J* = 5.3, 5.3 Hz, 1H, C_{29}-**H**), 3.46 (dd, *J* = 5.3, 2.2 Hz, 1H, C_{30}-**H**), 2.60 (d, *J* = 6.9 Hz, 1H, C_{28}-O**H**), 2.31 (ddd, *J* = 14.2, 7.2, 7.0 Hz, 1H, one of C_{32}-**H**), 2.23 (ddd, *J* = 14.1, 6.9, 6.3 Hz, 1H, one of C_{32}-**H**), 1.44 (s, 3H, one of C**H**$_3$), 1.37 (s, 3H, one of C**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.2, 137.8, 134.9, 128.5, 128.4, 128.3, 128.1, 128.0, 127.7, 117.4, 109.0, 79.5, 77.8, 76.0, 73.9, 73.9, 69.2, 66.0, 39.0, 26.5, 25.6; HRMS (ESI-TOF) *m/z* calcd for $C_{25}H_{33}O_5$ $[M+H]^+$: 413.2323, found: 413.2330.



(78) Benson, R.E.; McKusick, B.C. *Org. Synth.* **1958**, *38*, 78–84.

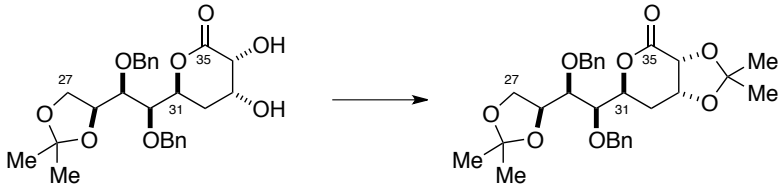
(1*R*,2*R*,3*S*)-1,2-Bis(benzyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)hex-5-en-3-yl acrylate (81). To a solution of homoallylic carbinol **64** (1.6 g, 4.0 mmol, 1.0 equiv) in THF (20 mL, 0.2 M wrt **64**) at room temperature was added EtN(*i*Pr)$_2$ (2.1 mL, 12 mmol, 3.0 equiv), DMAP (0.12 g, 0.99 mmol, 0.25 equiv), and a freshly prepared solution of acrylic pivalic anhydride in PhH (6.0 mL, 2.0 M, 12 mmol, 3.0 equiv). The resulting suspension was stirred at room temperature for 7 h, then charged with additional EtN(*i*Pr)$_2$ (2.1 mL, 12 mmol, 3.0 equiv), DMAP (0.12 g, 0.99 mmol, 0.25 equiv), and acrylic pivalic anhydride (6.0 mL, 2.0 M in PhH, 12 mmol, 3.0 equiv). The reaction mixture was stirred for an additional 12 h, quenched with sat. aq $NaHCO_3$ (35 mL), and diluted with Et_2O (35 mL) and H_2O (5 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 x 60 mL). The combined organic extracts were dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 6% → 8% → 10% EtOAc in hexanes) afforded acrylate ester **81** (1.48 g, 80% yield) as a clear, colorless oil. $[\alpha]_D^{25}$ –19.3° (*c* = 1.3, CH_2Cl_2); IR (neat) 3066, 3032, 2985, 2892, 1730 (s), 1640, 1497, 1455, 1405, 1371, 1260, 1195, 1064 (br), 987, 919, 853, 808, 736, 698 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.35–7.27 (m, 10H, Ar**H**), 6.42 (dd, *J* = 17.3, 1.2 Hz, 1H, one of C_{34a}-**H**), 6.14 (dd, *J* = 17.3, 10.4 Hz, 1H, C_{34}-**H**), 5.83 (dd, *J* = 10.4, 1.2 Hz, 1H, one of C_{34a}-**H**), 5.67 (dddd, *J* = 17.1, 10.1, 7.0, 7.0 Hz, 1H, C_{33}-**H**), 5.32 (ddd, *J* = 7.3, 5.2, 4.9 Hz, 1H, C_{31}-**H**), 5.02 (dd, *J* = 10.1, 1.5 Hz, 1H, one of C_{33a}-**H**), 4.99 (dd, *J* = 17.1, 1.5 Hz, 1H, one of C_{33a}-**H**), 4.74 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.72 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.64 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.58 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.26 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1H, C_{28}-**H**), 3.86 (dd, *J* = 8.3, 6.5 Hz, 1H, one of C_{27}-**H**), 3.73 (dd, *J* = 7.9, 7.6 Hz, 1H, one of C_{27}-**H**), 3.65 (dd, *J* = 5.0, 4.8 Hz, 1H, C_{30}-**H**), 3.51 (dd, *J* = 5.4, 5.4 Hz, 1H, C_{29}-**H**), 2.46 (dddd, *J* = 14.3, 6.6, 5.6, 1.0 Hz, 1H, one of C_{32}-**H**), 2.32 (ddd, *J* = 14.6, 7.5, 7.2 Hz, 1H, one of C_{32}-**H**), 1.43 (s, 3H, one of C**H**$_3$), 1.34 (s, 3H, one of C**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.5, 138.2, 137.9, 133.5, 131.1, 128.4, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 117.9, 109.0, 78.6, 78.0, 76.4, 74.0, 73.9, 72.5, 65.8, 35.4, 26.5, 25.6; HRMS (ESI-TOF) *m/z* calcd for $C_{28}H_{34}NaO_6$ $[M+Na]^+$: 489.2248, found: 489.2229.



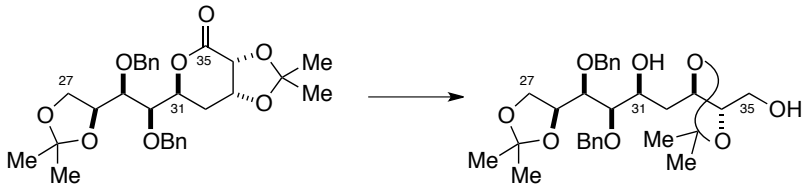
(*S*)-6-((1*R*,2*R*)-1,2-Bis(benzyloxy)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5,6-dihydro-2*H*-pyran-2-one (65). To a degassed solution of diene **81** (0.28 g, 0.60 mmol, 1.0 equiv) in PhH (40 mL, 0.015 M wrt **81**) at room temperature was added ruthenium catalyst **90** (0.025 g, 0.030 mmol, 0.05 equiv). The reaction mixture was purged with argon for 5 min, stirred at 65 °C for 12 h, then recharged with additional catalyst (0.025 g, 0.030 mmol, 0.05 equiv) at this time and approximately every 7 h twice after (total catalyst **90** added: 0.2 equiv). The reaction mixture was stirred at 65 °C for an additional 12 h, cooled to room temperature, concentrated to half volume, diluted with 2:1 hexanes/EtOAc (50 mL) and filtered through a silica gel plug (4 cm). The filter cake was rinsed with 2:1 hexanes/EtOAc (200 mL), and the filtrate concentrated. Column chromatography (gradient elution, 4:1 → 3:1 → 5:2 hexanes/EtOAc) afforded lactone **65** (0.23 g, 89% yield) as a dark brown oil contaminated with ruthenium-based impurities (<5%). A sufficient quantity of this material was repurified by column chromatography to produce a clear, colorless oil for characterization. $[\alpha]_D^{25}$ –91.0° (*c* = 1.2, CH_2Cl_2); IR (neat) 3064, 3031, 2986, 2935, 2881, 1732 (s), 1498, 1455, 1381, 1248, 1213, 1157, 1116, 1064, 893, 851, 816, 740, 700 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.36–7.28 (m, 10H, Ar**H**), 6.79 (ddd, *J* = 9.7, 6.3, 2.3 Hz, 1H, C_{33}-**H**), 5.97 (ddd, *J* = 9.7, 2.8, 0.7 Hz, 1H, C_{34}-**H**), 4.75 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.73 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.71 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.71 (ddd, *J* = 12.2, 4.2, 3.8 Hz, 1H, C_{31}-**H**), 4.67 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.39 (ddd, *J* = 6.9, 6.7, 5.1 Hz, 1H, C_{28}-**H**), 3.90 (dd, *J* = 8.2, 6.6 Hz, 1H, one of C_{27}-**H**), 3.79 (dd, *J* = 8.2, 7.0 Hz, 1H, one of C_{27}-**H**), 3.72 (dd, *J* = 5.3, 5.3 Hz, 1H, C_{29}-**H**), 3.61 (dd, *J* = 5.3, 4.2 Hz, 1H, C_{30}-**H**), 2.51 (dddd, *J* = 18.3, 12.2, 2.6, 2.5 Hz, 1H, one of C_{32}-**H**), 2.08 (dddd, *J* = 18.5, 6.2, 3.8, 0.9 Hz, 1H, one of C_{32}-**H**), 1.45 (s, 3H, one of C**H**$_3$), 1.35 (s, 3H, one of C**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.7, 145.5, 138.1, 137.6, 128.4, 128.4, 128.3, 128.1, 128.0, 127.8, 120.8, 109.2, 79.1, 78.0, 77.8, 76.3, 74.6, 74.2, 65.7, 26.5, 25.8, 25.6; HRMS (ESI-TOF) *m*/*z* calcd for $C_{26}H_{30}NaO_6$ $[M+Na]^+$: 461.1935, found: 461.1937.

(3*R*,4*R*,6*S*)-6-((1*R*,2*R*)-1,2-Bis(benzyloxy)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3,4-dihydroxytetrahydro-2*H*-pyran-2-one (82). To a bright yellow suspension of $NaIO_4$ (0.17 g, 0.80 mmol, 1.5 equiv) and $CeCl_3 \bullet 7H_2O$ (0.020 g, 0.053 mmol, 0.1 equiv) in deionized H_2O (0.53 mL, 1.5 M wrt $NaIO_4$) at 0 °C was added EtOAc (0.66 mL, 1.2 M wrt $NaIO_4$), MeCN (0.80 mL, 1.0 M wrt $NaIO_4$), and an aqueous solution of $RuCl_3$ (27 μL, 0.1 M, 2.7 μmol, 0.005 equiv). The bilayer suspension was stirred at 0 °C for 5 min, then charged slowly dropwise with a solution of unsaturated lactone **65** (0.23 g, 0.53 mmol, 1.0 equiv) in EtOAc (1.1 mL, 0.5 M wrt **65**) over 1 min (with 2 x 0.27 mL rinses). The reaction mixture was vigorously stirred at 0 °C for 1.5 h, charged with Na_2SO_4 (0.53 g), then filtered through Na_2SO_4 with EtOAc rinses (50 mL total) into a flask containing sat. aq Na_2SO_3 (10 mL) and brine (10 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4 with added hexanes (150 mL) and filtered through a silica gel plug (4 cm). The filter cake was rinsed with 1:1 hexanes/EtOAc (300 mL), and the filtrate concentrated and azeotroped with PhH (2 x 5 mL) to afford crude diol **82** (0.21 g, 85% yield) as a solid of mixed white and brown coloration due to contamination with ruthenium-based impurities (<5%). The crude product was analyzed by ^{1}H-NMR spectroscopy to assess reaction diastereoselectivity (d.r. ≥ 95:05). $[\alpha]_D^{24}$ –12.1° (*c* = 1.0, CH_2Cl_2); IR (neat) 3442 (br), 3064, 3030, 2965, 2934, 1745 (s), 1455, 1371, 1214, 1124, 1062, 854, 741, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.36–7.24 (m, 10H, Ar**H**), 5.03 (ddd, *J* = 11.4, 4.1, 2.2 Hz, 1H, C_{31}-**H**), 4.80 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.78 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.70 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.53 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.38 (ddd, *J* = 6.7, 6.6, 4.5 Hz, 1H, C_{28}-**H**), 4.29 (m, 1H, C_{33}-**H**), 4.05 (dd, *J* = 2.9, 1.0 Hz, 1H, C_{34}-**H**), 3.99 (dd, *J* = 8.2, 6.6 Hz, 1H, one of C_{27}-**H**), 3.87 (dd, *J* = 8.2, 6.9 Hz, 1H, one of C_{27}-**H**), 3.82 (dd, *J* = 6.7, 4.5 Hz, 1H, C_{29}-**H**), 3.57 (dd, *J* = 6.9, 2.3 Hz, 1H, C_{30}-**H**), 3.38 (d, *J* = 1.0 Hz, 1H, C_{34}-O**H**), 2.69 (dd, *J* = 2.1, 1.2 Hz, 1H, C_{33}-O**H**), 2.12 (dddd, *J* = 14.4, 11.4, 2.1, 2.1 Hz, 1H, one of C_{32}-**H**), 1.99 (ddd, *J* = 14.5, 4.2, 4.2

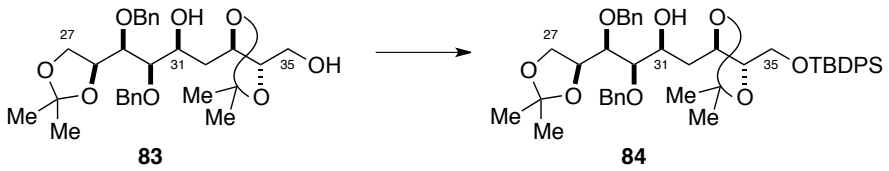
Hz, 1H, one of C_{32}-**H**), 1.45 (s, 3H, one of C**H**$_3$), 1.36 (s, 3H, one of C**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.7, 138.2, 137.4, 128.5, 128.4, 128.1, 128.1, 127.9, 127.7, 109.1, 80.0, 78.2, 76.9, 76.2, 74.8, 74.7, 70.4, 66.1, 65.5, 29.8, 26.5, 25.6; HRMS (ESI-TOF) *m/z* calcd for $C_{26}H_{32}NaO_8$ $[M+Na]^+$: 495.1989, found: 495.1999.



(3a*R*,6*S*,7a*R*)-6-((1*R*,2*R*)-1,2-Bis(benzyloxy)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4(6*H*)-one (66). To a solution of diol **82** (0.75 g, 1.6 mmol, 1.0 equiv) in 2:1 acetone/2,2-dimethoxypropane (32 mL, 0.05 M wrt **82**) at rt was added PPTS (40 mg, 0.16 mmol, 0.1 equiv). The reaction mixture was stirred at 30 °C for 15 h, quenched with a large spatula tip full of $NaHCO_3$ (s), stirred vigorously for an additional 15 min, and filtered through Celite®. The filter cake was rinsed with EtOAc (40 mL total), and the filtrate concentrated. Column chromatography (gradient elution, 16% → 18% → 20% EtOAc in hexanes) afforded acetonide **66** (0.63 g, 78% yield) as a white solid. $[\alpha]_D^{25}$ +6.5° (*c* = 1.1, CH_2Cl_2); IR (neat) 3031, 2987, 2936, 1751 (s), 1497, 1456, 1377, 1266, 1211, 1159, 1119, 1061, 919, 852, 738, 700 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.35–7.26 (m, 10H, Ar**H**), 4.92 (ddd, *J* = 10.4, 2.2, 2.1 Hz, 1H, C_{31}-**H**), 4.76 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.74 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.69 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.57 (m, *J* = 9.7, 2.8 Hz, 1H, C_{33}-**H**), 4.56 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.53 (dd, *J* = 6.9, 1.0 Hz, 1H, C_{34}-**H**), 4.35 (ddd, *J* = 6.4, 6.3, 4.8 Hz, 1H, C_{28}-**H**), 3.97 (dd, *J* = 7.3, 6.4 Hz, 1H, one of C_{27}-**H**), 3.84 (dd, *J* = 7.3, 7.3 Hz, 1H, one of C_{27}-**H**), 3.78 (dd, *J* = 5.9, 5.0 Hz, 1H, C_{29}-**H**), 3.61 (dd, *J* = 6.2, 3.2 Hz, 1H, C_{30}-**H**), 2.99 (ddd, *J* = 15.1, 10.3, 3.1 Hz, 1H, one of C_{32}-**H**), 1.88 (ddd, *J* = 15.1, 2.1, 1.8 Hz, 1H, one of C_{32}-**H**), 1.48 (s, 3H, one of C**H**$_3$), 1.44 (s, 3H, one of C**H**$_3$), 1.35 (s, 3H, one of C**H**$_3$), 1.33 (s, 3H, one of C**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.8, 138.1, 137.5, 128.5, 128.4, 128.2, 128.0, 127.9, 127.7, 110.6, 109.0, 80.1, 78.1, 76.1, 74.9, 74.6, 74.5, 72.9, 71.7, 65.5, 30.9, 26.5, 26.0, 25.6, 24.0; HRMS (ESI-TOF) *m/z* calcd for $C_{29}H_{36}KO_8$ $[M+K]^+$: 551.2042, found: 551.2039.



(2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-((4*R*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)butan-2-ol (83). To a solution of lactone **66** (0.64 g, 1.3 mmol, 1.0 equiv) in THF (13 mL, 0.10 M wrt **66**) at 0 °C was added H_2O (36 μL, 2.0 mmol, 1.6 equiv) and $LiBH_4$ (0.041 g, 1.9 mmol, 1.5 equiv). The reaction mixture was slowly warmed to rt o/n (16 h total stir time), then recooled to 0 °C, quenched with 1 M aq NaOH (15 mL), stirred vigorously at rt for 0.5 h, and diluted with Et_2O (15 mL). The layers were separated and the organic layer washed sequentially with H_2O and brine (10 mL each). The combined aqueous layers were extracted with Et_2O (2 x 15 mL), and the combined organic extracts were dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 2:1 → 1:1 → 1:2 hexanes/EtOAc + 1% Et_3N) afforded diol **83** (0.64 g, quant. yield) as a clear, colorless oil. $[\alpha]_D^{23}$ –10.1° (*c* = 2.7, CH_2Cl_2); IR (neat) 3480 (br), 3064, 3031, 2986, 2935, 2879, 1497, 1456, 1371, 1251, 1216, 1161, 1118, 1065, 892, 862, 737, 700 cm^{-1}; ^{1}H-NMR (600 MHz, C_6D_6) δ 7.38 (m, 2H, Ar**H**), 7.23–7.06 (m, 8H, Ar**H**), 4.77 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.70 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.63 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.62 (ddd, *J* = 7.2, 6.6, 5.0 Hz, 1H, C_{28}-**H**), 4.44 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.19 (dddd, *J* = 8.2, 4.2, 4.0, 3.4 Hz, 1H, C_{31}-**H**), 4.07 (ddd, *J* = 10.0, 5.9, 4.1 Hz, 1H, C_{33}-**H**), 3.95–3.90 (m, *J* = 8.2, 7.3, 6.6 Hz, 2H, C_{27}-**H**$_2$), 3.90 (m, *J* = 6.2, 3.1 Hz, 1H, C_{34}-**H**), 3.82 (dd, *J* = 5.6, 5.1 Hz, 1H, C_{29}-**H**), 3.60 (dd, *J* = 5.8, 3.0 Hz, 1H, C_{30}-**H**), 3.45–3.38 (m, *J* = 11.3, 7.2, 6.2, 5.4, 4.7 Hz, 2H, C_{35}-**H**$_2$), 3.08 (d, *J* = 4.5 Hz, 1H, C_{31}-O**H**), 1.98 (ddd, *J* = 14.1, 9.7, 8.5 Hz, 1H, one of C_{32}-**H**), 1.94 (dd, *J* = 7.2, 4.8 Hz, 1H, C_{35}-O**H**), 1.55 (ddd, *J* = 14.1, 4.0, 4.0 Hz, 1H, one of C_{32}-**H**), 1.52 (s, 3H, one of C**H**$_3$), 1.37 (s, 3H, one of C**H**$_3$), 1.33 (s, 3H, one of C**H**$_3$), 1.19 (s, 3H, one of C**H**$_3$); ^{13}C-NMR (125 MHz, C_6D_6) δ 139.3, 138.8, 128.6, 128.5, 128.5, 128.2, 128.0, 127.7, 109.1, 108.2, 81.4, 79.1, 78.3, 77.4, 76.0, 74.5, 74.2, 70.0, 66.3, 61.6, 33.3, 28.1, 26.9, 26.0, 25.4; HRMS (ESI-TOF) *m/z* calcd for $C_{29}H_{41}O_8$ $[M+H]^+$: 517.2796, found: 517.2800.



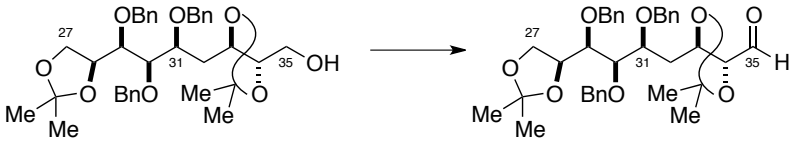
(2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-1-((4*R*,5*S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butan-2-ol (84). To a solution of diol **83** (0.60 g, 1.2 mmol, 1.0 equiv) and imidazole (0.12 g, 1.7 mmol, 1.5 equiv) in DMF (5.8 mL, 0.20 M wrt **83**) at 0 °C was added *tert*-butylchlorodiphenylsilane (0.33 mL, 1.3 mmol, 1.1 equiv). The reaction mixture was stirred at 0 °C for 4 h, quenched with sat. aq $NaHCO_3$ (15 mL), and diluted with 1:1 hexanes/Et_2O (30 mL) and H_2O (5 mL). The layers were separated and the aqueous layer extracted with 1:1 hexanes/Et_2O (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Column chromatography (gradient elution, 12% → 16% → 20% EtOAc in hexanes) afforded silyl ether **84** (0.83 g, 95% yield) as a clear, colorless oil. $[\alpha]_D^{24}$ –7.2° (*c* = 2.8, CH_2Cl_2); IR (neat) 3522 (br), 3070, 3030, 2985, 2933, 2859, 1455, 1428, 1380, 1360, 1252, 1216, 1113, 1066, 824, 738 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.71 (m, 5H, Ar**H**), 7.49–7.29 (m, 15H, Ar**H**), 4.77 (d, *J* = 12.2 Hz, 1H, one of –OC**H**$_2$Ph), 4.75 (d, *J* = 12.3 Hz, 1H, one of –OC**H**$_2$Ph), 4.70 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.57 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.50 (ddd, *J* = 6.9, 6.7, 5.7 Hz, 1H, C_{28}-**H**), 4.23 (ddd, *J* = 10.8, 6.0, 2.3 Hz, 1H, C_{33}-**H**), 4.15 (ddd, *J* = 6.4, 6.3, 6.0 Hz, 1H, C_{34}-**H**), 4.13 (m, *J* = 8.1, 3.4 Hz, 1H, C_{31}-**H**), 3.97 (dd, *J* = 8.1, 6.6 Hz, 1H, one of C_{27}-**H**), 3.85 (dd, *J* = 7.8, 7.8 Hz, 1H, one of C_{27}-**H**), 3.69 (dd, *J* = 5.4, 5.4 Hz, 1H, C_{29}-**H**), 3.66 (dd, *J* = 10.8, 6.8 Hz, 1H, one of C_{35}-**H**), 3.63 (dd, *J* = 10.7, 5.7 Hz, 1H, one of C_{35}-**H**), 3.49 (dd, *J* = 5.4, 2.9 Hz, 1H, C_{30}-**H**), 3.26 (d, *J* = 3.2 Hz, 1H, C_{31}-O**H**), 1.87 (ddd, *J* = 14.2, 10.8, 8.5 Hz, 1H, one of C_{32}-**H**), 1.69 (ddd, *J* = 14.1, 3.2, 2.9 Hz, 1H, one of C_{32}-**H**), 1.49 (s, 3H, one of C**H**$_3$), 1.42 (s, 3H, one of C**H**$_3$), 1.41 (s, 3H, one of C**H**$_3$), 1.35 (s, 3H, one of C**H**$_3$), 1.10 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.5, 137.9, 135.6, 135.5, 133.3, 133.1, 129.8, 129.8, 128.4, 128.3, 128.3, 128.0, 127.8, 127.7, 127.7, 127.6, 108.8, 108.4, 80.6, 78.4, 78.0, 76.8, 76.4, 74.1, 74.0, 70.0, 65.9, 62.7, 32.8, 28.0, 26.8, 26.6, 25.7, 25.4, 19.2; HRMS (ESI-TOF) *m/z* calcd for $C_{45}H_{58}NaO_8Si$ $[M+Na]^+$: 777.3793, found: 777.3797.

***tert*-Butyl(((4*S*,5*R*)-2,2-dimethyl-5-((2*S*,3*R*,4*R*)-2,3,4-tris(benzyloxy)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butyl)-1,3-dioxolan-4-yl)methoxy)diphenylsilane (61).** To a solution of carbinol **84** (0.83 g, 1.1 mmol, 1.0 equiv) in DMF (5.5 mL, 0.20 M wrt **84**) at –20 °C was added sodium hydride (0.13 g, 60 wt% mineral oil dispersion, 3.3 mmol, 3.0 equiv). The suspension was stirred at –20 °C for 15 min, then charged with benzyl bromide (0.20 mL, 1.6 mmol, 1.5 equiv) and tetrabutylammonium iodide (0.041 g, 0.11 mmol, 0.1 equiv). The reaction mixture was stirred at –20 °C for 3 h, briefly warmed to 0 °C, then quenched with sat. aq NH_4Cl (15 mL), and diluted with 1:1 hexanes/Et_2O (40 mL) and H_2O (5 mL). The layers were separated and the aqueous layer extracted with 1:1 hexanes/Et_2O (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Column chromatography (gradient elution, 6% → 8% → 10% EtOAc in hexanes) afforded benzyl ether **61** (0.88 g, 95% yield) as a clear, colorless oil. $[\alpha]_D^{25}$ +10.4° (*c* = 0.94, CH_2Cl_2); IR (neat) 3069, 3030, 2985, 2933, 2859, 1496, 1455, 1428, 1370, 1253, 1212, 1109, 1071, 823, 739 cm^{-1}; ^{1}H-NMR (600 MHz, C_6D_6) δ 7.81–7.79 (m, 4H, Ar**H**), 7.42 (m, *J* = 7.3 Hz, 2H, Ar**H**), 7.30 (m, *J* = 7.2 Hz, 2H, Ar**H**), 7.25 (m, *J* = 7.2 Hz, 2H, Ar**H**), 7.22–7.04 (m, 15H, Ar**H**), 4.98 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.83 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.70 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.65 (ddd, *J* = 7.0, 6.7, 6.7 Hz, 1H, C_{28}-**H**), 4.58 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.54 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.44 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.35 (ddd, *J* = 10.5, 6.4, 1.8 Hz, 1H, C_{33}-**H**), 4.23 (ddd, *J* = 8.8, 3.7, 3.4 Hz, 1H, C_{31}-**H**), 4.10 (ddd, *J* = 6.0, 6.0, 5.6 Hz, 1H, C_{34}-**H**), 3.96 (dd, *J* = 6.6, 4.2 Hz, 1H, C_{29}-**H**), 3.91 (dd, *J* = 7.9, 7.6 Hz, 1H, one of C_{27}-**H**), 3.86 (m, *J* = 4.1 Hz, 1H, C_{30}-**H**), 3.85 (dd, *J* = 8.2, 6.4 Hz, 1H, one of C_{27}-**H**), 3.82 (dd, *J* = 10.8, 6.3 Hz, 1H, one of C_{35}-**H**), 3.77 (dd, *J* = 10.7, 5.2 Hz, 1H, one of C_{35}-**H**), 2.18 (ddd, *J* = 14.4, 7.1, 1.8 Hz, 1H, one of C_{32}-**H**), 1.94 (ddd, *J* = 14.5, 10.7, 3.4 Hz, 1H, one of C_{32}-**H**), 1.51 (s, 3H, one of C**H**$_3$), 1.44 (s, 3H, one of C**H**$_3$), 1.34 (s, 3H, one of C**H**$_3$), 1.27 (s, 3H, one of C**H**$_3$), 1.16 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C-NMR (125 MHz, C_6D_6) δ 139.7, 139.3, 139.2, 136.1, 136.0, 133.8, 133.7, 130.1, 128.5, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.7, 109.0, 108.0, 79.7, 79.3, 78.5,

78.4, 77.8, 74.1, 74.0, 73.7, 72.0, 66.3, 63.6, 29.6, 28.3, 27.1, 25.9, 25.5, 19.4; HRMS (ESI-TOF) *m/z* calcd for $C_{52}H_{64}O_8Si$ $[M+H]^+$: 845.4443, found: 845.4456.

((4*S*,5*R*)-2,2-Dimethyl-5-((2*S*,3*R*,4*R*)-2,3,4-tris(benzyloxy)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butyl)-1,3-dioxolan-4-yl)methanol (85). To a solution of silyl ether **61** (0.88 g, 1.0 mmol, 1.0 equiv) in THF (6.9 mL, 0.15 M wrt **61**) at 0 °C was added dropwise a solution of tetrabutylammonium fluoride in THF (1.6 mL, 1.0 M, 1.6 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 8 h, slowly warmed to rt over 6 h, then quenched with sat. aq $NaHCO_3$ (15 mL), and diluted with Et_2O (35 mL) and H_2O (5 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 x 35 mL). The combined organic extracts were dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 4:1 → 2:1 hexanes/EtOAc + 1% Et_3N) afforded carbinol **85** (0.63 g, quant. yield) as a clear, colorless oil. $[\alpha]_D^{24}$ +6.4° (*c* = 0.81, CH_2Cl_2); IR (neat) 3478 (br), 3063, 3030, 2985, 2935, 2880, 1496, 1454, 1370, 1251, 1213, 1160, 1064, 916, 855, 736 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.36–7.27 (m, 15H, Ar**H**), 4.81 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.75 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.69 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.65 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.57 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.55 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.23 (ddd, *J* = 7.2, 6.7, 6.7 Hz, 1H, C_{28}-**H**), 4.01 (ddd, *J* = 10.1, 6.3, 2.9 Hz, 1H, C_{33}-**H**), 3.84 (ddd, *J* = 6.2, 5.9, 4.2 Hz, 1H, C_{31}-**H**), 3.79 (ddd, *J* = 6.2, 5.9, 4.2 Hz, 1H, C_{34}-**H**), 3.59 (dd, *J* = 6.7, 4.0 Hz, 1H, C_{29}-**H**), 3.54 (dd, *J* = 7.9, 7.5 Hz, 1H, one of C_{27}-**H**), 3.52 (dd, *J* = 5.9, 4.0 Hz, 1H, C_{30}-**H**), 3.44 (dd, *J* = 8.1, 6.4 Hz, 1H, one of C_{27}-**H**), 3.31 (m, *J* = 11.3, 7.6, 7.2, 4.5, 4.4 Hz, 2H, C_{35}-**H**$_2$), 1.74 (dd, *J* = 7.8, 4.5 Hz, 1H, C_{35}-O**H**), 1.60 (ddd, *J* = 14.5, 6.4, 2.9 Hz, 1H, one of C_{32}-**H**), 1.43 (s, 3H, one of C**H**$_3$), 1.41 (s, 3H, one of C**H**$_3$), 1.36 (ddd, *J* = 14.5, 10.1, 4.1 Hz, 1H, one of C_{32}-**H**), 1.29 (s, 3H, one of C**H**$_3$), 1.29 (s, 3H, one of C**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.6, 138.3, 138.1, 129.0, 128.5, 128.4, 128.4, 128.3, 128.0, 127.8, 127.6, 108.8, 108.0, 77.8, 77.7, 77.7,

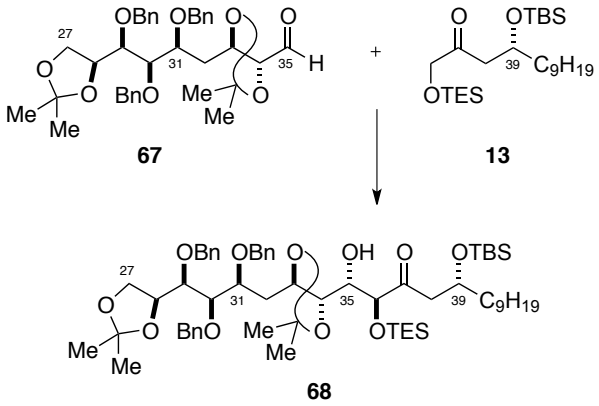
76.7, 73.8, 73.4, 72.8, 72.2, 65.6, 61.7, 28.6, 28.2, 26.7, 25.5, 25.4; HRMS (ESI-TOF) *m/z* calcd for $C_{36}H_{46}NaO_8$ $[M+Na]^+$: 629.3085, found: 629.3104.



(4*R*,5*R*)-2,2-Dimethyl-5-((2*S*,3*R*,4*R*)-2,3,4-tris(benzyloxy)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butyl)-1,3-dioxolane-4-carbaldehyde (67). To a solution of carbinol **85** (0.12 g, 0.19 mmol, 1.0 equiv) and $EtN(iPr)_2$ (0.10 mL, 0.58 mmol, 3.0 equiv) in CH_2Cl_2 (0.55 mL, 0.35 M wrt **85**) and DMSO (0.22 mL, 0.88 M wrt **85**) at –30 °C was added a solution of SO_3•py (0.093 g, 0.58 mmol, 3.0 equiv) in DMSO (0.33 mL, 1.75 M wrt SO_3•py). The reaction mixture was stirred between –30 °C and –20 °C for 1.5 h, then quenched with brine (20 mL), Et_2O (60 mL) and H_2O (2 mL). The layers were separated and the organic layer washed sequentially with 1 M aq $NaHSO_4$ (20 mL), sat. aq $NaHCO_3$ (20 mL), and 1:1 H_2O/brine (2 x 20 mL). The organic layer was then dried over Na_2SO_4 with added hexanes, filtered and concentrated to afford crude aldehyde **67** (0.11 g, 96% yield) as a clear, colorless oil that was used without further purification. $[\alpha]_D^{25}$ +7.4° (*c* = 0.94, CH_2Cl_2); IR (neat) 3063, 3030, 2986, 2934, 1734 (s), 1496, 1454, 1370, 1255, 1216, 1159, 1065, 858, 736, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.38 (d, *J* = 3.2 Hz, 1H, C_{35}-**H**), 7.35–7.28 (m, 15H, Ar**H**), 4.80 (d, *J* = 12.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.75 (d, *J* = 12.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.72 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.62 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.56 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.54 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.24 (ddd, *J* = 7.2, 6.9, 6.9 Hz, 1H, C_{28}-**H**), 4.19 (ddd, *J* = 10.0, 7.3, 2.8 Hz, 1H, C_{33}-**H**), 3.88 (dd, *J* = 7.2, 3.4 Hz, 1H, C_{34}-**H**), 3.86 (ddd, *J* = 6.2, 6.2, 4.2 Hz, 1H, C_{31}-**H**), 3.56 (dd, *J* = 7.0, 3.6 Hz, 1H, C_{29}-**H**), 3.51 (dd, *J* = 7.9, 7.8 Hz, 1H, one of C_{27}-**H**), 3.46 (dd, *J* = 6.2, 3.6 Hz, 1H, C_{30}-**H**), 3.42 (dd, *J* = 8.1, 6.4 Hz, 1H, one of C_{27}-**H**), 1.75 (ddd, *J* = 14.6, 6.3, 2.8 Hz, 1H, one of C_{32}-**H**), 1.52 (s, 3H, one of C**H**$_3$), 1.43 (s, 3H, one of C**H**$_3$), 1.33 (s, 3H, one of C**H**$_3$), 1.30 (s, 3H, one of C**H**$_3$), 1.21 (ddd, *J* = 14.6, 10.1, 4.2 Hz, 1H, one of C_{32}-**H**); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 201.7, 138.4, 138.1, 138.0, 128.9, 128.7, 128.4, 128.4, 128.3, 128.3, 128.0, 127.8, 127.8, 110.5, 108.9, 81.7, 77.9, 77.7, 77.4, 76.4, 74.4, 73.7, 73.3, 72.3, 65.6, 29.3, 27.6, 26.7,

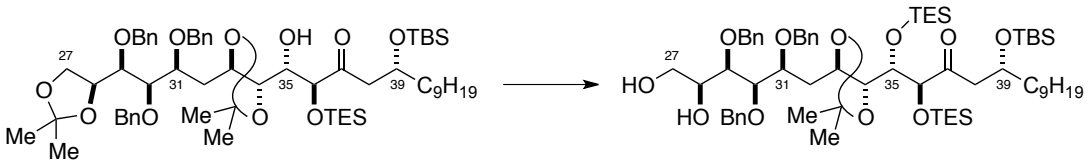
25.5, 25.3; HRMS (ESI-TOF) *m/z* calcd for $C_{36}H_{44}NaO_8$ [M+Na]$^+$: 627.2928, found: 627.2914.

Synthesis of the C27–C48 Aldehyde



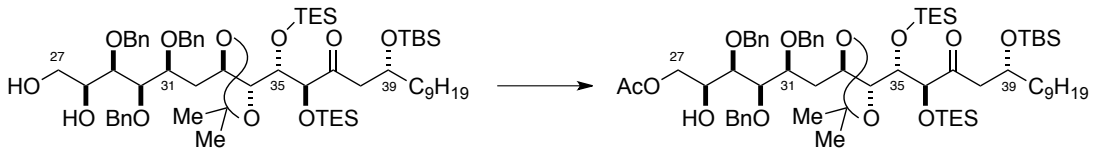
(5*S*,8*R*)-5-((*S*)-((4*S*,5*R*)-2,2-Dimethyl-5-((2*S*,3*R*,4*R*)-2,3,4-tris(benzyloxy)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butyl)-1,3-dioxolan-4-yl)(hydroxy)methyl)-3,3-diethyl-10,10,11,11-tetramethyl-8-nonyl-4,9-dioxa-3,10-disiladodecan-6-one (68). To a solution of ketone **13** (0.29 g, 0.62 mmol, 2.0 equiv) and $EtNMe_2$ (0.14 mL, 1.2 mmol, 4.0 equiv) in pentane (3.1 mL, 0.2 M wrt **13**) at 0 °C was added Cy_2BCl (0.14 mL, 0.65 mmol, 2.1 equiv). The enolization mixture was stirred at 0 °C for 20 min, then stirred at rt for 15 h, then cooled to –78 °C and charged slowly dropwise with a solution of aldehyde **67** (0.19 g, 0.31 mmol, 1.0 equiv) in Et_2O (0.70 mL, 0.44 M wrt **67**) over 1 min (with 0.30 mL rinse). The reaction mixture was stirred at –78 °C for 0.5 h, slowly warmed to –40 °C over 0.5 h, stirred at –40 °C for 4 h, slowly warmed to –25 °C over 2 h, stirred at –25 °C for 9 h, then quenched at 0 °C with aq pH 7 buffer (3 mL), MeOH (3 mL), Et_2O (15 mL) and 30% aq H_2O_2 (1 mL). The biphasic mixture was stirred vigorously at 0 °C for 0.5 h, then at rt for 1 h. The layers were separated and the aqueous layer extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with 10% aq $Na_2S_2O_3$ (2 x 10 mL) and brine (10 mL), dried over Na_2SO_4 with added hexanes, filtered and concentrated. The residue was analyzed by ^{1}H-NMR spectroscopy to assess reaction diastereoselectivity (d.r. = 91:09). Column chromatography (gradient elution, 5% → 6% EtOAc in hexanes) afforded aldol adduct **68** (0.26 g, 77% yield) as a clear, colorless oil. $[\alpha]_D^{25}$ +0.2° (*c* = 1.7, CH_2Cl_2); IR (neat) 3567 (br), 3065, 3031, 2929, 2856, 1721 (s), 1497, 1456, 1379, 1253, 1211, 1159, 1074, 836, 776, 733, 699 cm^{-1}; ^{1}H-NMR

(600 MHz, $CDCl_3$) δ 7.35–7.26 (m, 15H, Ar**H**), 4.82 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.71 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.70 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.68 (d, *J* = 12.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.60 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.53 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.23 (dddd, *J* = 6.2, 6.0, 5.4, 5.4 Hz, 1H, C_{39}-**H**), 4.18 (ddd, *J* = 7.0, 6.9, 6.7 Hz, 1H, C_{28}-**H**), 4.07 (m, *J* = 8.5, 7.6 Hz, 1H, C_{33}-**H**), 4.03 (m, *J* = 7.3 Hz, 1H, C_{34}-**H**), 3.90 (m, *J* = 3.4 Hz, 1H, C_{31}-**H**), 3.88 (d, *J* = 8.6 Hz, 1H, C_{36}-**H**), 3.62 (dd, *J* = 6.7, 4.0 Hz, 1H, C_{29}-**H**), 3.57 (dd, *J* = 5.3, 4.1 Hz, 1H, C_{30}-**H**), 3.53 (dd, *J* = 7.9, 7.8 Hz, 1H, one of C_{27}-**H**), 3.42 (dd, *J* = 7.9, 6.7 Hz, 1H, one of C_{27}-**H**), 3.37 (dd, *J* = 8.8, 8.8 Hz, 1H, C_{35}-**H**), 2.92 (dd, *J* = 18.5, 5.6 Hz, 1H, one of C_{38}-**H**), 2.65 (dd, *J* = 18.4, 6.8 Hz, 1H, one of C_{38}-**H**), 2.13 (d, *J* = 8.9 Hz, 1H, C_{35}-O**H**), 1.88 (ddd, *J* = 14.5, 10.4, 3.2 Hz, 1H, one of C_{32}-**H**), 1.74 (ddd, *J* = 14.5, 7.0, 1.8 Hz, 1H, one of C_{32}-**H**), 1.53 (m, *J* = 5.0 Hz, 1H, one of C_{40}-**H**), 1.43 (s, 3H, one of C**H**$_3$), 1.42–1.37 (m, 1H, one of C_{40}-**H**), 1.40 (s, 3H, one of C**H**$_3$), 1.36–1.23 (m, 14H, $C_{41–47}$-**H**$_2$), 1.27 (s, 3H, one of C**H**$_3$), 1.26 (s, 3H, one of C**H**$_3$), 0.97 (t, *J* = 8.0 Hz, 9H, –$SiCH_2C$**H**$_3$), 0.88 (s, 9H, C(C**H**$_3$)$_3$), 0.88 (t, *J* = 7.2 Hz, 3H, C_{48}-**H**$_3$), 0.64 (q, *J* = 7.9 Hz, 6H, –SiC**H**$_2$$CH_3$), 0.09 (s, 3H, one of SiC**H**$_3$), 0.06 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 210.1, 138.8, 138.4, 138.2, 129.0, 128.3, 128.3, 128.3, 128.2, 127.9, 127.7, 127.5, 108.7, 107.6, 78.7, 78.3, 77.8, 77.6, 76.9, 74.8, 73.8, 73.6, 72.9, 71.9, 71.1, 67.6, 65.5, 45.8, 37.5, 31.9, 29.7, 29.6, 29.6, 29.3, 26.8, 26.7, 25.9, 25.5, 25.0, 24.3, 22.7, 18.0, 14.1, 6.7, 4.7, –4.5, –4.7; HRMS (ESI-TOF) *m/z* calcd for $C_{61}H_{98}NaO_{11}Si_2$ $[M+Na]^+$: 1085.6540, found: 1085.6487.



(5*R*,8*S*,9*S*)-9-((4*R*,5*R*)-2,2-Dimethyl-5-((2*S*,3*R*,4*R*,5*S*)-2,3,4-tris(benzyloxy)-5,6-dihydroxyhexyl)-1,3-dioxolan-4-yl)-11,11-diethyl-2,2,3,3-tetramethyl-5-nonyl-8-((triethylsilyl)oxy)-4,10-dioxa-3,11-disilatridecan-7-one (69). To a solution of carbinol **68** (0.25 g, 0.24 mmol, 1.0 equiv) and 2,6-lutidine (0.16 mL, 1.4 mmol, 6.0 equiv) in CH_2Cl_2 (2.4 mL, 0.1 M wrt **68**) at 0 °C was added TESOTf (0.11 mL, 0.47 mmol, 2.0 equiv). The reaction mixture was stirred at 0 °C for 3 h, charged with TMSOTf (85 μL, 0.47 mmol, 2.0 equiv),

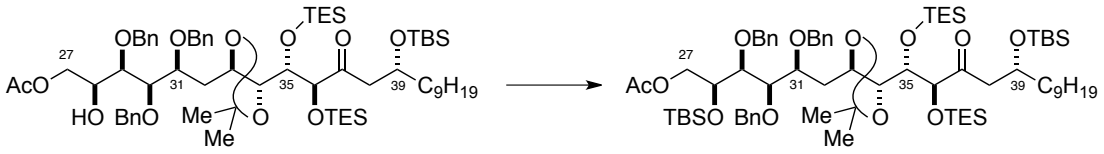
stirred at 0 °C for an additional 3 h, then quenched with 1 M aq H_2SO_4 (8 mL) and Et_2O (8 mL). The biphasic mixture was stirred vigorously at 0 °C for 0.5 h, then diluted with H_2SO_4 (10 mL) and Et_2O (30 mL), and the layers were separated. The organic layer was washed sequentially with sat. aq $NaHCO_3$ and brine (10 mL each), dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 4:1 → 3:1 hexanes/EtOAc) afforded diol **69** (0.24 g, 88% yield) as a clear, colorless oil. $[\alpha]_D^{26}$ +18.8° (*c* = 1.4, CH_2Cl_2); IR (neat) 3440 (br), 3065, 3032, 2955, 2929, 2878, 1712 (s), 1456, 1378, 1250, 1220, 1100, 1061, 837, 775, 732, 699 cm^{-1}; ^{1}H-NMR (600 MHz, C_6D_6) δ 7.40 (m, *J* = 7.9, 0.9 Hz, 2H, Ar**H**), 7.35 (m, *J* = 7.9, 0.9 Hz, 2H, Ar**H**), 7.23–7.07 (m, 11H, Ar**H**), 4.76 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.74 (d, *J* = 12.3 Hz, 1H, one of –OC**H**$_2$Ph), 4.68 (ddd, *J* = 11.9, 5.1, 2.8 Hz, 1H, C_{33}-**H**), 4.62 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.58 (m, *J* = 5.9, 5.9 Hz, 1H, C_{39}-**H**), 4.56 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.52 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.49 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.30 (dd, *J* = 9.2, 5.1 Hz, 1H, C_{34}-**H**), 4.18 (ddd, *J* = 8.9, 4.5, 2.9 Hz, 1H, C_{31}-**H**), 4.13 (dd, *J* = 9.2, 2.1 Hz, 1H, C_{35}-**H**), 4.08 (dd, *J* = 7.2, 2.8 Hz, 1H, C_{30}-**H**), 4.03 (d, *J* = 2.1 Hz, 1H, C_{36}-**H**), 4.02 (dd, *J* = 7.2, 4.0 Hz, 1H, C_{29}-**H**), 3.97 (m, *J* = 4.5, 4.2 Hz, 1H, C_{28}-**H**), 3.71 (m, *J* = 10.8, 5.6 Hz, 1H, one of C_{27}-**H**), 3.67 (m, 1H, one of C_{27}-**H**), 3.26 (dd, *J* = 19.5, 6.0 Hz, 1H, one of C_{38}-**H**), 3.19 (dd, *J* = 19.5, 6.0 Hz, 1H, one of C_{38}-**H**), 2.89 (d, *J* = 5.1 Hz, 1H, C_{28}-O**H**), 2.16 (ddd, *J* = 12.6, 12.3, 4.5 Hz, 1H, one of C_{32}-**H**), 2.06 (ddd, *J* = 12.7, 9.1, 2.8 Hz, 1H, one of C_{32}-**H**), 1.78 (m, *J* = 5.6 Hz, 1H, C_{27}-O**H**), 1.76 (m, 1H, one of C_{40}-**H**), 1.69 (m, 1H, one of C_{40}-**H**), 1.60–1.51 (m, 2H, C_{41}-**H**$_2$), 1.43 (s, 3H, one of C**H**$_3$), 1.42–1.23 (m, 12H, $C_{42–47}$-**H**$_2$), 1.28 (s, 3H, one of C**H**$_3$), 1.16 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H**$_3$), 1.03 (s, 9H, C(C**H**$_3$)$_3$), 0.96 (t, *J* = 8.0 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.92–0.80 (m, *J* = 8.1 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.91 (t, *J* = 6.7 Hz, 3H, C_{48}-**H**$_3$), 0.62–0.52 (m, *J* = 8.1, 7.9 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.22 (s, 3H, one of SiC**H**$_3$), 0.21 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, C_6D_6) δ 211.6, 139.2, 139.0, 138.9, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.1, 127.9, 127.6, 108.2, 79.5, 79.4, 79.3, 79.0, 76.4, 75.9, 74.7, 74.4, 74.3, 72.2, 72.0, 67.7, 64.1, 49.1, 38.5, 30.6, 30.3, 30.1, 30.0, 29.8, 28.8, 26.1, 26.1, 25.6, 23.1, 18.3, 14.3, 7.3, 7.1, 5.7, 5.0, –4.2, –4.4; HRMS (ESI-TOF) *m/z* calcd for $C_{64}H_{108}NaO_{11}Si_3$ $[M+Na]^+$: 1159.7092, found: 1159.7053.



69 **86**

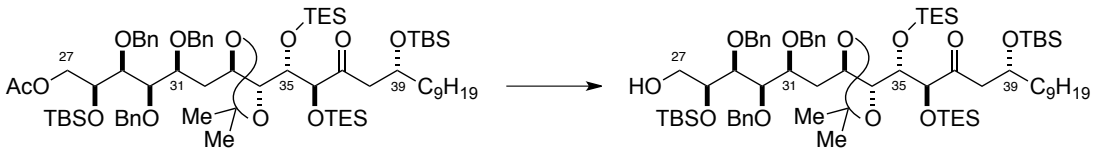
(2*S*,3*R*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-6-((4*R*,5*R*)-5-((5*S*,6*S*,9*R*)-3,3-diethyl-11,11,12,12-tetramethyl-9-nonyl-7-oxo-6-((triethylsilyl)oxy)-4,10-dioxa-3,11-disilatridecan-5-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyhexyl acetate (86). To a solution of diol **69** (0.22 g, 0.19 mmol, 1.0 equiv) and 2,4,6-collidine (51 μL, 0.38 mmol, 2.0 equiv) in CH_2Cl_2 (0.96 mL, 0.2 M wrt **69**) at –78 °C was added acetyl chloride (18 μL, 0.25 mmol, 1.3 equiv). The reaction mixture was stirred at –78 °C for 2 h, slowly warmed to 0 °C over 2 h, then quenched at 0 °C with 1 M aq H_2SO_4 (1 mL) and Et_2O (1 mL). The biphasic mixture was stirred vigorously while warming to rt over 5 min, then diluted with H_2SO_4 (10 mL) and Et_2O (40 mL), and the layers were separated. The organic layer was washed with 1:1 sat. aq $NaHCO_3$/brine (15 mL), dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 12% → 14% → 16% EtOAc in hexanes) afforded acetate ester **86** (0.22 g, 98% yield) as a clear, colorless oil. $[\alpha]_D^{26}$ +16.6° (*c* = 2.7, CH_2Cl_2); IR (neat) 3467 (br), 3064, 3032, 2930, 1743 (s), 1717 (s), 1458, 1375, 1247, 1096, 1062, 981, 838, 733, 700 cm^{-1}; ^{1}H-NMR (600 MHz, C_6D_6) δ 7.38 (m, *J* = 7.5 Hz, 2H, Ar**H**), 7.36 (m, *J* = 7.3 Hz, 2H, Ar**H**), 7.22–7.06 (m, 11H, Ar**H**), 4.74 (d, *J* = 10.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.74 (d, *J* = 12.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.67 (ddd, *J* = 12.0, 5.1, 2.8 Hz, 1H, C_{33}-**H**), 4.64 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.60 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.56 (m, *J* = 5.9, 5.7, 5.6 Hz, 1H, C_{39}-**H**), 4.52 (d, *J* = 11.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.48 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.36 (dd, *J* = 11.1, 6.9 Hz, 1H, one of C_{27}-**H**), 4.29 (dd, *J* = 9.0, 4.8 Hz, 1H, C_{34}-**H**), 4.28 (dd, *J* = 11.3, 5.9 Hz, 1H, one of C_{27}-**H**), 4.19 (m, *J* = 7.3, 7.0, 2.8 Hz, 1H, C_{28}-**H**), 4.17 (m, *J* = 8.8, 4.5 Hz, 1H, C_{31}-**H**), 4.13 (dd, *J* = 9.4, 1.9 Hz, 1H, C_{35}-**H**), 4.11 (dd, *J* = 9.1, 2.6 Hz, 1H, C_{30}-**H**), 4.03 (dd, *J* = 7.6, 2.6 Hz, 1H, C_{29}-**H**), 4.02 (d, *J* = 1.9 Hz, 1H, C_{36}-**H**), 3.24 (dd, *J* = 19.5, 6.0 Hz, 1H, one of C_{38}-**H**), 3.23 (dd, *J* = 19.5, 5.9 Hz, 1H, one of C_{38}-**H**), 2.75 (d, *J* = 7.3 Hz, 1H, C_{28}-O**H**), 2.18 (ddd, *J* = 12.6, 12.2, 4.5 Hz, 1H, one of C_{32}-**H**), 2.08 (ddd, *J* = 12.7, 8.8, 2.5 Hz, 1H, one of C_{32}-**H**), 1.74 (m, 1H, one of C_{40}-**H**), 1.68 (m, 1H, one of C_{40}-**H**), 1.62 (s, 3H, COC**H**$_3$), 1.60–1.50 (m, 2H, C_{41}-**H**$_2$), 1.42 (s, 3H, one of

C**H**$_3$), 1.40–1.24 (m, 12H, $C_{42–47}$-**H**$_2$), 1.28 (s, 3H, one of C**H**$_3$), 1.16 (t, J = 7.9 Hz, 9H, –SiCH$_2$C**H**$_3$), 1.02 (s, 9H, C(C**H**$_3$)$_3$), 0.95 (t, J = 7.9 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.93–0.79 (m, J = 7.9 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.90 (t, J = 6.8 Hz, 3H, C_{48}-**H**$_3$), 0.60–0.53 (m, J = 8.1, 7.8 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.21 (s, 3H, one of SiC**H**$_3$), 0.20 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, C_6D_6) δ 211.6, 170.2, 139.2, 138.8, 138.7, 128.6, 128.5, 128.5, 128.4, 128.3, 127.9, 127.6, 127.5, 108.2, 79.5, 79.3, 79.3, 79.1, 76.5, 75.9, 74.9, 74.4, 74.4, 71.9, 69.9, 67.7, 66.0, 49.1, 38.4, 32.3, 30.4, 30.3, 30.1, 30.0, 29.8, 28.8, 26.1, 26.0, 25.6, 23.1, 20.4, 18.3, 14.3, 7.3, 7.1, 5.7, 5.0, –4.2, –4.4; HRMS (ESI-TOF) *m/z* calcd for $C_{66}H_{110}NaO_{12}Si_3$ [M+Na]$^+$: 1201.7197, found: 1201.7193.



(2*S*,3*S*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-6-((4*R*,5*R*)-5-((5*S*,6*S*,9*R*)-3,3-diethyl-11,11,12,12-tetramethyl-9-nonyl-7-oxo-6-((triethylsilyl)oxy)-4,10-dioxa-3,11-disilatridecan-5-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)hexyl acetate (70). To a solution of carbinol **86** (0.22 g, 0.19 mmol, 1.0 equiv) and 2,6-lutidine (88 μL, 0.75 mmol, 4.0 equiv) in CH_2Cl_2 (0.94 mL, 0.2 M wrt **86**) at 0 °C was added TBSOTf (86 μL, 0.38 mmol, 2.0 equiv). The reaction mixture was stirred at 0 °C for 4 h, slowly warmed to rt over 4 h, stirred at rt for 2 h, then quenched at 0 °C with sat. aq $NaHCO_3$ (2 mL) and Et_2O (1 mL). The biphasic mixture was stirred vigorously while warming to rt over 5 min, then diluted with H_2O (10 mL) and Et_2O (40 mL), and the layers were separated. The organic layer was washed sequentially with 1 M aq $NaHSO_4$ and 1:1 sat. aq $NaHCO_3$/brine (15 mL each), dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 2% → 3% → 4% EtOAc in hexanes) afforded acetate ester **70** (0.18 g, 74% yield) as a clear, colorless oil. $[\alpha]_D^{26}$ +10.4° (c = 2.8, CH_2Cl_2); IR (neat) 3066, 3032, 2930, 2857, 1745 (s), 1714 (s), 1456, 1369, 1251, 1101, 1055, 1008, 979, 836, 777, 732, 698 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.35–7.15 (m, 15H, Ar**H**), 4.77 (d, J = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.66 (d, J = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.62 (d, J = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.59 (d, J = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.56 (d, J = 11.3 Hz, 1H, one of –OC**H**$_2$Ph), 4.45 (d, J

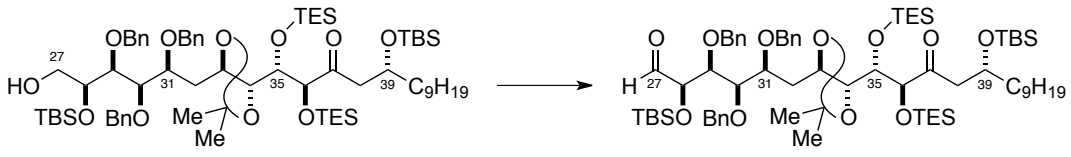
= 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.28 (dd, *J* = 11.3, 3.7 Hz, 1H, one of C_{27}-**H**), 4.24 (ddd, *J* = 7.0, 6.7, 6.0 Hz, 1H, C_{33}-**H**), 4.20 (dddd, *J* = 6.0, 5.9, 5.6, 5.4 Hz, 1H, C_{39}-**H**), 4.10 (dd, *J* = 11.3, 6.9 Hz, 1H, one of C_{27}-**H**), 3.92 (m, *J* = 3.7 Hz, 1H, C_{28}-**H**), 3.92 (m, *J* = 4.8 Hz, 1H, C_{31}-**H**), 3.91 (dd, *J* = 5.1, 3.8 Hz, 1H, C_{29}-**H**), 3.84 (dd, *J* = 5.1, 5.0 Hz, 1H, C_{30}-**H**), 3.82 (dd, *J* = 8.9, 5.1 Hz, 1H, C_{34}-**H**), 3.76 (dd, *J* = 9.1, 1.9 Hz, 1H, C_{35}-**H**), 3.65 (d, *J* = 1.9 Hz, 1H, C_{36}-**H**), 2.86 (dd, *J* = 19.6, 6.6 Hz, 1H, one of C_{38}-**H**), 2.81 (dd, *J* = 19.6, 5.4 Hz, 1H, one of C_{38}-**H**), 1.89 (m, 1H, one of C_{32}-**H**), 1.89 (s, 3H, COC**H**$_3$), 1.79 (m, *J* = 7.0, 6.0 Hz, 1H, one of C_{32}-**H**), 1.46–1.20 (m, 16H, $C_{40–47}$-**H**$_2$), 1.39 (s, 3H, one of C**H**$_3$), 1.24 (s, 3H, one of C**H**$_3$), 0.95 (t, *J* = 8.0 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.86 (t, *J* = 7.2 Hz, 3H, C_{48}-**H**$_3$), 0.86 (s, 9H, one of C(C**H**$_3$)$_3$), 0.84 (s, 9H, one of C(C**H**$_3$)$_3$), 0.83 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.68–0.55 (m, *J* = 7.9, 7.8, 7.5 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.48–0.40 (m, *J* = 8.1, 7.9 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.06 (s, 3H, one of SiC**H**$_3$), 0.01 (s, 3H, one of SiC**H**$_3$), –0.02 (s, 3H, one of SiC**H**$_3$), –0.02 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 212.0, 170.7, 138.8, 138.6, 138.4, 128.3, 128.2, 128.2, 128.1, 127.7, 127.5, 127.4, 127.3, 107.6, 78.7, 78.6, 78.5, 77.3, 76.1, 75.3, 73.9, 73.9, 73.9, 71.3, 71.3, 67.3, 66.6, 48.7, 37.9, 31.9, 30.4, 29.8, 29.6, 29.6, 29.3, 28.7, 25.9, 25.9, 25.8, 25.2, 22.7, 20.9, 18.1, 18.0, 14.1, 6.9, 6.8, 5.1, 4.5, –4.5, –4.5, –4.5, –4.7; HRMS (ESI-TOF) *m/z* calcd for $C_{72}H_{124}NaO_{12}Si_4$ $[M+Na]^+$: 1315.8062, found: 1315.8075.



70 **87**

(5*R*,8*S*,9*S*)-9-((4*R*,5*R*)-2,2-Dimethyl-5-((2*S*,3*R*,4*S*,5*S*)-2,3,4-tris(benzyloxy)-5-((*tert*-butyldimethylsilyl)oxy)-6-hydroxyhexyl)-1,3-dioxolan-4-yl)-11,11-diethyl-2,2,3,3-tetramethyl-5-nonyl-8-((triethylsilyl)oxy)-4,10-dioxa-3,11-disilatridecan-7-one (87). To a solution of acetate ester **70** (0.14 g, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (2.2 mL, 0.05 M wrt **70**) at –78 °C was added dropwise a solution of DIBALH in PhMe (0.15 mL, 1.0 M, 0.15 mmol, 1.4 equiv). The reaction mixture was stirred at –78 °C for 15 min, then quenched sequentially at –78 °C with EtOAc (0.15 mL), sat. aq Rochelle's salt (5 mL), and CH_2Cl_2 (2 mL). The biphasic mixture was stirred vigorously at rt for 2 h, then diluted with H_2O (10 mL) and CH_2Cl_2 (30 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x

30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Column chromatography (gradient elution, 3% → 4% → 5% EtOAc in hexanes) afforded carbinol **87** (0.12 g, 84% yield) as a clear, colorless oil. $[\alpha]_D^{25}$ +19.6° (*c* = 1.8, CH_2Cl_2); IR (neat) 3510 (br), 3065, 3031, 2930, 2857, 1711 (s), 1461, 1408, 1378, 1252, 1219, 1098, 1061, 1008, 836, 776, 732, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.32–7.20 (m, 15H, Ar**H**), 4.80 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.66 (m, 2H, –OC**H**$_2$Ph), 4.63 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.56 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.50 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.28 (ddd, *J* = 11.1, 5.0, 3.1 Hz, 1H, C_{33}-**H**), 4.22 (dddd, *J* = 6.0, 5.7, 5.6, 5.4 Hz, 1H, C_{39}-**H**), 3.98 (ddd, *J* = 4.1, 4.0, 3.5 Hz, 1H, C_{31}-**H**), 3.92 (dd, *J* = 4.4, 4.0 Hz, 1H, C_{30}-**H**), 3.91 (dd, *J* = 6.0, 5.0 Hz, 1H, C_{29}-**H**), 3.84 (m, *J* = 5.3, 5.0 Hz, 1H, C_{28}-**H**), 3.84 (dd, *J* = 8.8, 5.0 Hz, 1H, C_{34}-**H**), 3.77 (dd, *J* = 8.9, 1.9 Hz, 1H, C_{35}-**H**), 3.69 (ddd, *J* = 11.3, 8.2, 3.1 Hz, 1H, one of C_{27}-**H**), 3.67 (d, *J* = 1.9 Hz, 1H, C_{36}-**H**), 3.56 (ddd, *J* = 11.4, 5.1, 4.7 Hz, 1H, one of C_{27}-**H**), 2.89 (dd, *J* = 19.6, 6.7 Hz, 1H, one of C_{38}-**H**), 2.82 (dd, *J* = 19.6, 5.3 Hz, 1H, one of C_{38}-**H**), 1.78 (dd, *J* = 8.1, 4.7 Hz, 1H, C_{27}-O**H**), 1.75 (ddd, *J* = 13.0, 11.1, 4.2 Hz, 1H, one of C_{32}-**H**), 1.71 (m, *J* = 13.0, 2.8 Hz, 1H, one of C_{32}-**H**), 1.48–1.22 (m, 16H, C_{40-47}-**H**$_2$), 1.42 (s, 3H, one of C**H**$_3$), 1.26 (s, 3H, one of C**H**$_3$), 0.97 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.89 (s, 9H, one of C(C**H**$_3$)$_3$), 0.88 (t, 3H, C_{48}-**H**$_3$), 0.87 (s, 9H, one of C(C**H**$_3$)$_3$), 0.84 (t, *J* = 8.0 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.70–0.57 (m, *J* = 7.8, 7.5, 7.3 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.43 (q, *J* = 7.9 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.08 (s, 3H, one of SiC**H**$_3$), 0.04 (s, 3H, one of SiC**H**$_3$), 0.01 (s, 3H, one of SiC**H**$_3$), –0.01 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.9, 138.8, 138.6, 138.3, 128.4, 128.2, 128.2, 128.2, 128.0, 127.5, 127.4, 127.4, 127.3, 107.7, 78.8, 78.6, 78.5, 77.5, 76.1, 75.3, 74.1, 73.9, 73.5, 73.3, 71.4, 67.3, 64.2, 48.7, 37.9, 31.9, 30.4, 29.8, 29.6, 29.6, 29.3, 28.7, 26.0, 25.9, 25.9, 25.2, 22.7, 18.1, 18.0, 14.1, 6.9, 6.8, 5.3, 5.1, 5.0, 4.5, –4.5, –4.5, –4.7, –4.7; HRMS (ESI-TOF) *m/z* calcd for $C_{70}H_{122}NaO_{11}Si_4$ $[M+Na]^+$: 1273.7956, found: 1273.7948.

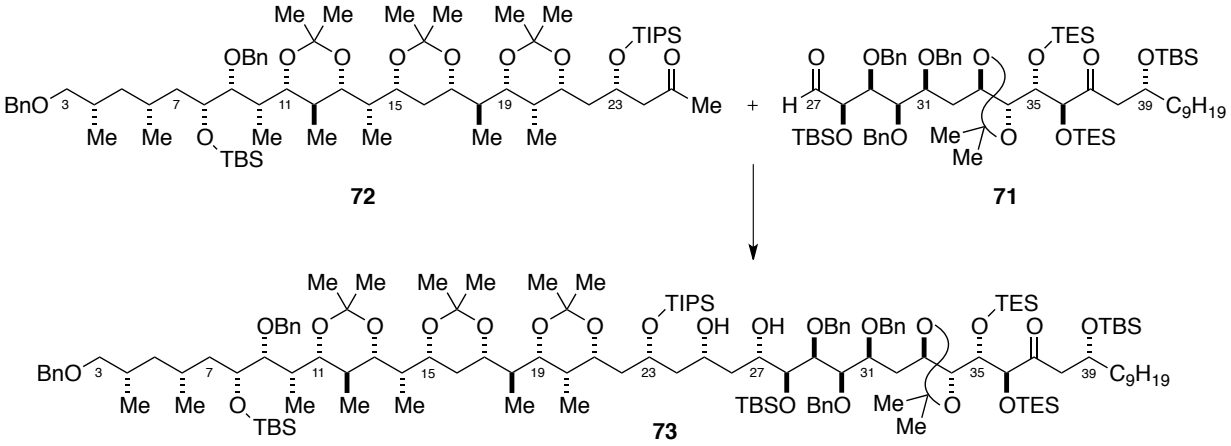


(2*R*,3*S*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-6-((4*R*,5*R*)-5-((5*S*,6*S*,9*R*)-3,3-diethyl-11,11,12,12-tetramethyl-9-nonyl-7-oxo-6-((triethylsilyl)oxy)-4,10-dioxa-3,11-disilatridecan-5-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)hexanal (71). To a solution of carbinol **87** (0.24 g, 0.19 mmol, 1.0 equiv) and EtN(*i*Pr)$_2$ (0.10 mL, 0.58 mmol, 3.0 equiv) in CH_2Cl_2 (0.55 mL, 0.35 M wrt **87**) and DMSO (0.11 mL, 1.8 M wrt **87**) at –30 °C was added a solution of SO_3•py (0.092 g, 0.58 mmol, 3.0 equiv) in DMSO (0.44 mL, 1.3 M wrt SO_3•py). The reaction mixture was stirred between –30 °C and –20 °C for 1.5 h, quenched with brine (15 mL), then diluted with Et_2O (40 mL) and H_2O (1 mL). The layers were separated and the organic layer washed sequentially with 1 M aq $NaHSO_4$ (15 mL), sat. aq $NaHCO_3$ (15 mL), and 1:1 H_2O/brine (2 x 15 mL). The organic layer was then dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 1% → 1.5% → 2% EtOAc in hexanes) afforded aldehyde **71** (0.23 g, 95% yield) as a clear, colorless oil. $[\alpha]_D^{26}$ +11.9° (*c* = 2.2, CH_2Cl_2); IR (neat) 3066, 3031, 2927, 2872, 1731 (s), 1714 (s), 1455, 1416, 1380, 1252, 1220, 1143, 1097, 1061, 1026, 979, 950, 894, 837, 777, 729, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.74 (s, 1H, C_{27}-**H**), 7.33–7.18 (m, 15H, Ar**H**), 4.68 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.63 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.61 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.47 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.46 (d, *J* = 11.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.32 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.25 (dddd, *J* = 5.7, 5.7, 5.7, 5.7 Hz, 1H, C_{39}-**H**), 4.22 (ddd, *J* = 11.4, 5.0, 2.1 Hz, 1H, C_{33}-**H**), 4.08 (dd, *J* = 5.9, 3.7 Hz, 1H, C_{29}-**H**), 3.97 (d, *J* = 5.7 Hz, 1H, C_{28}-**H**), 3.88 (dd, *J* = 5.6, 3.7 Hz, 1H, C_{30}-**H**), 3.84 (dd, *J* = 9.1, 5.1 Hz, 1H, C_{34}-**H**), 3.79 (m, 1H, C_{31}-**H**), 3.78 (dd, *J* = 9.1, 2.0 Hz, 1H, C_{35}-**H**), 3.70 (d, *J* = 2.1 Hz, 1H, C_{36}-**H**), 2.90 (dd, *J* = 19.6, 6.4 Hz, 1H, one of C_{38}-**H**), 2.85 (dd, *J* = 19.6, 5.6 Hz, 1H, one of C_{38}-**H**), 1.87 (ddd, *J* = 13.9, 3.7, 1.6 Hz, 1H, one of C_{32}-**H**), 1.75 (ddd, *J* = 13.8, 11.9, 5.0 Hz, 1H, one of C_{32}-**H**), 1.48–1.27 (m, 16H, $C_{40–47}$-**H$_2$**), 1.41 (s, 3H, one of C**H**$_3$), 1.27 (s, 3H, one of C**H**$_3$), 0.97 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H$_3$**), 0.89 (t, *J* = 7.0 Hz, 3H, C_{48}-**H$_3$**), 0.88 (s, 9H, one of C(C**H**$_3$)$_3$), 0.88 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H$_3$**), 0.88 (s, 9H, one of C(C**H**$_3$)$_3$), 0.71–0.59 (m, *J* = 8.1, 7.9, 7.8 Hz, 6H, –SiC**H$_2$**CH$_3$), 0.43 (q, *J* = 7.9 Hz, 6H, –SiC**H$_2$**CH$_3$), 0.09 (s, 3H, one of SiC**H**$_3$), 0.06 (s, 3H, one of SiC**H**$_3$), 0.02 (s, 3H, one of SiC**H**$_3$), –0.10 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.9, 200.6, 138.7, 138.0, 137.7, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.7, 127.5, 127.4, 107.6, 80.9, 78.8, 78.4, 77.0, 76.9, 76.7, 75.3, 74.9, 73.7, 73.7, 72.1, 67.3, 48.7, 37.9, 31.9, 31.0, 29.8, 29.6,

29.6, 29.3, 28.6, 26.1, 25.9, 25.8, 25.2, 22.7, 18.3, 18.0, 14.1, 6.9, 6.8, 5.1, 4.5, –4.5, –4.6, –4.7, –5.5; HRMS (ESI-TOF) *m/z* calcd for $C_{70}H_{120}NaO_{11}Si_4$ $[M+Na]^+$: 1271.7800, found: 1271.7846.

Synthesis of the Aflastatin A C3–C48 Degradation Products

Magnesium bromide diethyl etherate ($MgBr_2$•OEt_2).[79] Magnesium turnings (99.98%) (2.3 g, 95 mmol, 1.0 equiv) were added to a two-necked round-bottomed flask, equipped with a reflux condenser and a magnetic stir bar. Diethyl ether (150 mL) was added, followed by a small amount of 1,2-dibromoethane. After refluxing was initiated by external heating, the remaining 1,2-dibromoethane (8.2 mL, 95 mmol, 1.0 equiv) was added portion-wise such that a moderate reflux was maintained. After completion of the reaction, excess diethyl ether was removed under a stream of nitrogen, yielding a white paste. The surface of the paste was broken with a spatula and the residue further dried with a stream of nitrogen. This process was repeated until a white solid was obtained. The compound was stored under argon at room temperature.



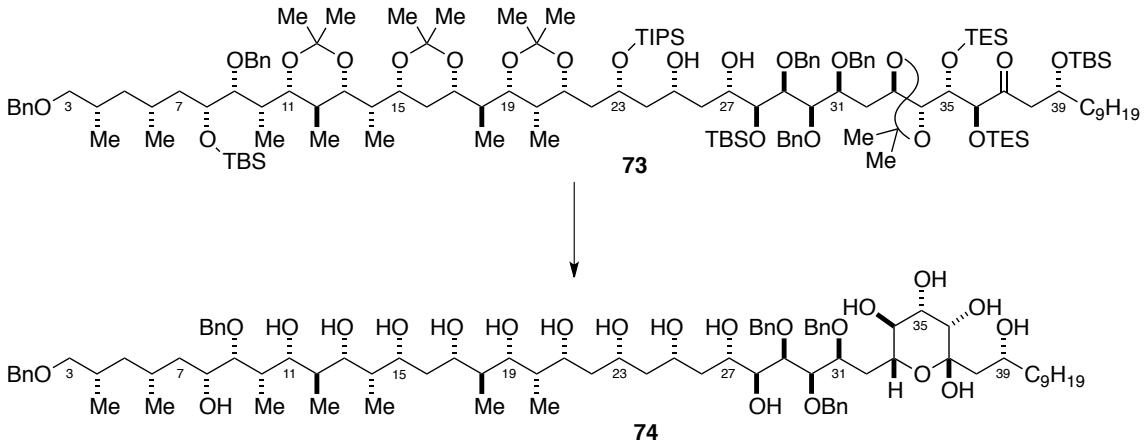
(5*R*,8*S*,9*S*)-9-((4*R*,5*R*)-2,2-Dimethyl-5-((2*S*,3*R*,4*S*,5*S*,6*S*,8*R*,10*R*)-2,3,4-tris(benzyloxy)-11-((4*R*,5*S*,6*S*)-6-((*S*)-1-((4*S*,6*R*)-6-((*S*)-1-((4*R*,5*R*,6*R*)-6-((2*S*,3*R*,4*R*,6*R*,8*S*)-3,9-bis(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)-6,8-dimethylnonan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-5-((*tert*-butyldimethylsilyl)oxy)-6,8-dihydroxy-10-((triisopropylsilyl)oxy)undecyl)-1,3-

(79) Harwood, L.M.; Manage, A.C.; Robin, S.; Hopes, S.F.G.; Watkin, D.J.; Williams, C.E. *Synlett* **1993**, 777–780.

dioxolan-4-yl)-11,11-diethyl-2,2,3,3-tetramethyl-5-nonyl-8-((triethylsilyl)oxy)-4,10-dioxa-3,11-disilatridecan-7-one (73). To a solution of aldehyde **71** (0.23 g, 0.18 mmol, 1.0 equiv) and ketone **72** (0.24 g, 0.20 mmol, 1.1 equiv) in CH_2Cl_2 (1.3 mL, 0.14 M wrt **71**) at –5 °C was added freshly prepared $MgBr_2$•OEt_2 (0.38 g, 1.5 mmol, 8.0 equiv). The resulting suspension was stirred at –5 °C for 10 min, then charged dropwise with 1,2,2,6,6-pentamethylpiperidine (83 μL, 0.46 mmol, 2.5 equiv). The reaction mixture was stirred at –5 °C for 7 min, then rapidly quenched with pre-chilled sat. aq $NaHCO_3$ (3 mL). The biphasic mixture was stirred vigorously at rt for 10 min, then diluted with Et_2O (30 mL), H_2O (10 mL) and sat. aq $NaHCO_3$ (15 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed sequentially with sat. aq NH_4Cl (2 x 20 mL) and brine (15 mL), dried over Na_2SO_4, filtered, concentrated and azeotroped with PhH (2 x 2 mL) to afford crude aldol adduct **88** as a clear, pale yellow oil that was used without further purification.

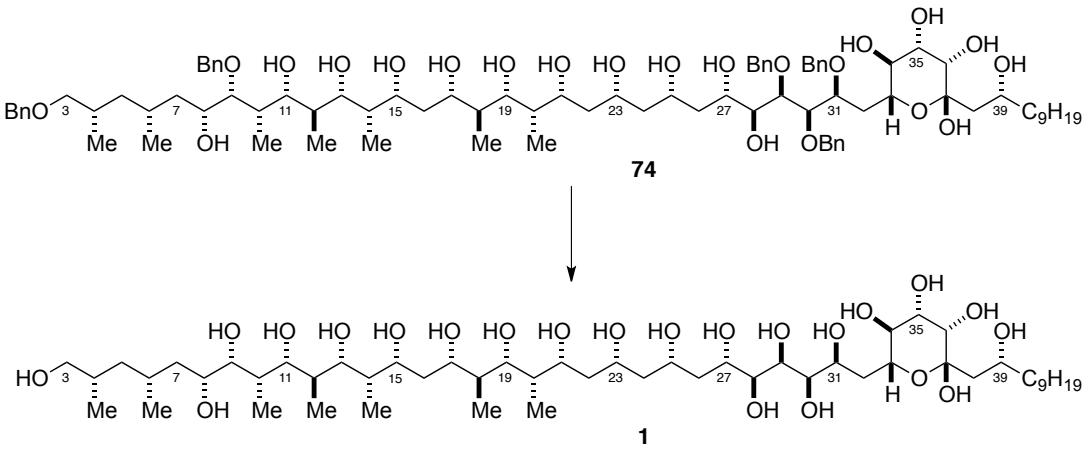
To a solution of crude aldol adduct **88** (theoretical 0.44 g, 0.18 mmol, 1.0 equiv) in 4:1 THF/MeOH (1.8 mL, 0.1 M wrt **88**) at –78 °C was added dropwise a solution of diethylmethoxyborane in THF (0.20 mL, 1.0 M, 0.20 mmol, 1.1 equiv). The reaction mixture was stirred at –78 °C for 2.5 h, then charged with sodium borohydride (21 mg, 0.55 mmol, 3.0 equiv) in one portion. The reaction mixture was slowly warmed to –55 °C over 0.5 h, stirred at –55 °C for 20 h, quenched with a pre-mixed mixture of 1 M aq NaOH (1 mL) and 30% aq H_2O_2 (0.4 mL), then diluted with 4:1 THF/MeOH (1 mL). The heterogeneous mixture was stirred vigorously at 0 °C for 1.5 h, then diluted with Et_2O (30 mL) and aq pH 7 buffer (3 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with 10% aq $Na_2S_2O_3$ (2 x 10 mL) and brine (10 mL), dried over Na_2SO_4 with added hexanes, filtered and concentrated. The residue was analyzed by ^{1}H-NMR spectroscopy to assess reaction diastereoselectivity (d.r. ≥ 95:05). Column chromatography (gradient elution, 6% → 6.5% EtOAc in hexanes) afforded diol **73** (0.31 g, 70% yield, two steps) as a white foam. $[\alpha]_D^{25}$ +1.0° (*c* = 1.2, CH_2Cl_2); IR (neat) 3498 (br), 3068, 3036, 2932, 2864, 1712, 1459, 1380, 1253, 1202, 1175, 1098, 1008, 982, 837, 775, 733, 698 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.34–7.21 (m, 25H, Ar**H**), 4.73 (d, *J* = 12.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.70 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.70 (d, *J* = 11.9 Hz, 1H, one

of –OC**H**$_2$Ph), 4.66 (m, 2H, –OC**H**$_2$Ph), 4.61 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.52 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.49 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.45 (m, 2H, –OC**H**$_2$Ph), 4.28 (ddd, *J* = 11.6, 7.0, 2.5 Hz, 1H, C_{33}-**H**), 4.25 (m, *J* = 7.0, 6.0 Hz, 1H), 4.22 (m, 1H), 4.21 (m, *J* = 5.1, 5.1 Hz, 1H, C_{39}-**H**), 4.18–4.16 (m, 2H), 4.03–3.98 (m, 2H), 3.98–3.92 (m, 3H), 3.91 (m, 1H, C_{31}-**H**), 3.88 (m, 1H, C_8-**H**), 3.82 (dd, *J* = 8.9, 4.9 Hz, 1H, C_{34}-**H**), 3.79 (dd, *J* = 8.9, 1.9 Hz, 1H, C_{35}-**H**), 3.69 (m, 1H), 3.66 (d, *J* = 1.9 Hz, 1H, C_{36}-**H**), 3.60 (m, *J* = 1.6 Hz, 1H), 3.59 (m, *J* = 9.8 Hz, 1H), 3.54 (m, *J* = 7.2, 2.8 Hz, 2H), 3.40 (dd, *J* = 6.2, 2.6 Hz, 1H, C_9-**H**), 3.33 (dd, *J* = 9.1, 5.3 Hz, 1H, one of C_3-**H**), 3.14 (dd, *J* = 9.1, 7.4 Hz, 1H, one of C_3-**H**), 2.88 (dd, *J* = 19.6, 6.6 Hz, 1H, one of C_{38}-**H**), 2.83 (dd, *J* = 19.5, 5.4 Hz, 1H, one of C_{38}-**H**), 2.39 (m, *J* = 6.8, 6.6, 2.5 Hz, 1H, C_{10}-**H**), 1.94–1.80 (m, 4H), 1.80–1.57 (m, 8H), 1.52 (m, *J* = 1.9 Hz, 1H), 1.48–1.20 (m, 16H, $C_{40–47}$-**H$_2$**), 1.48–1.20 (m, 5H), 1.44 (s, 3H, one of C**H**$_3$), 1.39 (s, 3H, one of C**H**$_3$), 1.37 (s, 3H, one of C**H**$_3$), 1.37 (s, 3H, one of C**H**$_3$), 1.37 (s, 3H, one of C**H**$_3$), 1.35 (s, 3H, one of C**H**$_3$), 1.31 (s, 3H, one of C**H**$_3$), 1.24 (s, 3H, one of C**H**$_3$), 1.16 (ddd, *J* = 13.3, 8.0, 5.6 Hz, 1H), 1.07 (m, 18H, –SiCH(C**H**$_3$)$_2$), 1.07 (m, 3H, –SiC**H**(CH$_3$)$_2$), 1.04 (ddd, *J* = 13.3, 6.3, 2.2 Hz, 1H), 0.99–0.97 (m, *J* = 6.9 Hz, 6H, two of –CH(C**H**$_3$)), 0.96 (t, *J* = 8.0 Hz, 9H, –SiCH$_2$C**H$_3$**), 0.92–0.81 (m, 12H, four of –CH(C**H**$_3$)), 0.88 (s, 9H, one of C(C**H**$_3$)$_3$), 0.88 (t, *J* = 7.1 Hz, 3H, C_{48}-**H$_3$**), 0.86 (s, 9H, one of C(C**H**$_3$)$_3$), 0.84 (s, 9H, one of C(C**H**$_3$)$_3$), 0.83 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H$_3$**), 0.73 (d, *J* = 6.9 Hz, 3H, one of –CH(C**H**$_3$)), 0.70–0.58 (m, *J* = 7.9, 7.8 Hz, 6H, –SiC**H$_2$**CH$_3$), 0.43 (q, *J* = 8.0 Hz, 6H, –SiC**H$_2$**CH$_3$), 0.07 (s, 3H, one of SiC**H**$_3$), 0.03 (s, 3H, one of SiC**H**$_3$), 0.03 (s, 3H, one of SiC**H**$_3$), 0.01 (s, 3H, one of SiC**H**$_3$), –0.03 (s, 3H, one of SiC**H**$_3$), –0.13 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.8, 139.8, 138.8, 138.8, 137.9, 137.7, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.8, 127.4, 127.4, 127.4, 127.3, 127.3, 127.0, 107.5, 98.3, 98.3, 97.2, 80.9, 79.6, 78.9, 78.5, 77.2, 75.9, 75.9, 75.8, 75.5, 75.0, 74.8, 74.0, 73.6, 73.3, 73.0, 72.8, 72.8, 72.5, 71.5, 71.5, 71.0, 69.9, 69.7, 68.2, 67.3, 67.2, 48.7, 45.1, 42.5, 40.8, 40.7, 39.2, 39.1, 38.6, 37.9, 32.7, 32.4, 31.9, 31.9, 31.3, 30.6, 30.4, 30.1, 30.0, 29.8, 29.6, 29.6, 29.3, 28.6, 27.1, 27.0, 26.0, 26.0, 25.9, 25.8, 25.2, 22.7, 20.7, 20.1, 19.8, 19.3, 18.2, 18.2, 18.2, 18.0, 18.0, 14.1, 12.7, 11.0, 9.5, 9.0, 8.9, 6.9, 6.8, 5.1, 4.6, 4.5, –3.7, –3.8, –4.2, –4.4, –4.5, –4.7; HRMS (ESI-TOF) *m/z* calcd for $C_{139}H_{242}NaO_{22}Si_6$ $[M+Na]^+$: 2454.6326, found: 2454.6361.



(2*S*,3*R*,4*R*,5*S*,6*S*,8*S*,10*R*,12*R*,13*S*,14*R*,15*S*,16*S*,18*R*,19*S*,20*R*,21*R*,22*R*,23*S*,24*R*,25*R*,27*R*,29*S*)-2,3,4,24,30-Pentakis(benzyloxy)-13,15,19,21,23,27,29-heptamethyl-1-((2*R*,3*S*,4*S*,5*S*,6*S*)-3,4,5,6-tetrahydroxy-6-((*R*)-2-hydroxyundecyl)tetrahydro-2*H*-pyran-2-yl)triacontan-5,6,8,10,12,14,16,18,20,22,25-undecaol (74). To a solution of ketone **73** (70 mg, 29 μmol, 1.0 equiv) in 1:1 CH_3CN/CH_2Cl_2 (1 mL, 0.03 M wrt **73**) at 0 °C was added dropwise a solution of fluorosilicic acid (H_2SiF_6) in H_2O (~60 μL, 20–25 wt. %). The reaction mixture was stirred at 0 °C for 0.5 h, then warmed to rt and stirred for 12 h, carefully quenched with two small spatula tips full of $NaHCO_3$ (s), stirred vigorously for an additional 1 h, and filtered through Celite®. The filter cake was rinsed with 1:1 EtOAc/CH_3OH (20 mL total), and the filtrate concentrated. Pipette column chromatography (gradient elution, 2.5% → 3% → 3.5% CH_3OH in CH_2Cl_2) afforded lactol **74** (0.034 g, 58% yield) as a clear, colorless oil. $[\alpha]_D^{24}$ –9.0° (*c* = 0.61, CH_3OH); IR (neat) 3377 (br), 3062, 3032, 2926, 2855, 1455, 1383, 1327, 1274, 1209, 1155, 1094, 1068, 1030, 970, 850, 736, 699 cm^{-1}; ^{1}H-NMR (600 MHz, CD_3OD) δ 7.46–7.20 (m, 25H, Ar**H**), 4.88 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.84 (d, *J* = 10.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.77 (d, *J* = 11.3 Hz, 1H, one of –OC**H**$_2$Ph), 4.71 (d, *J* = 10.5 Hz, 1H, one of –OC**H**$_2$Ph), 4.67 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.60 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.50 (d, *J* = 11.4 Hz, 2H, two of –OC**H**$_2$Ph), 4.45 (m, 2H, two of –OC**H**$_2$Ph), 4.32 (m, *J* = 8.8 Hz, 1H), 4.08–4.00 (m, 4H), 3.99–3.95 (m, 3H), 3.97 (m, 1H, C_{31}-**H**), 3.91 (m, *J* = 9.1, 1.2 Hz, 1H), 3.88–3.83 (m, 2H), 3.86 (m, 1H, C_{33}-**H**), 3.84 (dd, *J* = 9.5, 3.2 Hz, 1H, C_{35}-**H**), 3.80 (m, *J* = 8.6, 2.1 Hz, 1H), 3.65 (m, *J* = 9.4, 1.9 Hz, 1H), 3.65 (d, *J* = 3.4 Hz, 1H, C_{36}-**H**), 3.47 (dd, *J* = 9.5, 9.4 Hz, 1H, C_{34}-**H**), 3.34 (dd, *J* = 9.2, 5.3 Hz,

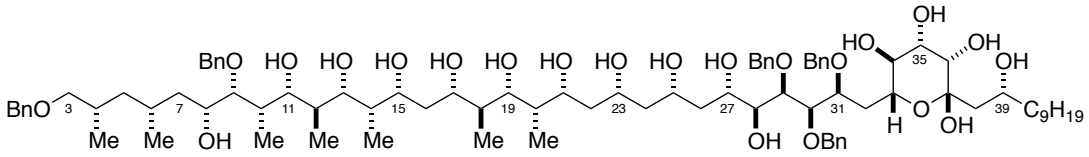
1H, one of C_3-**H**), 3.32 (m, *J* = 4.4, 1.8 Hz, 1H), 3.23 (dd, *J* = 9.2, 6.6 Hz, 1H, one of C_3-**H**), 3.20 (m, *J* = 9.4 Hz, 1H), 2.54 (ddd, *J* = 10.0, 10.0, 2.4 Hz, 1H, one of C_{32}-**H**), 2.25 (m, *J* = 7.0, 6.6, 6.3 Hz, 1H, C_{10}-**H**), 2.03 (dd, *J* = 14.5, 2.0 Hz, 1H, one of C_{38}-**H**), 2.01–1.97 (m, 1H), 1.99 (ddd, *J* = 10.0, 7.2, 7.1 Hz, 1H, one of C_{32}-**H**), 1.83 (m, *J* = 6.6, 6.2 Hz, 1H, one of C_4-**H**), 1.82–1.73 (m, 4H), 1.69–1.38 (m, 14H), 1.58 (dd, *J* = 14.4, 10.8 Hz, 1H, one of C_{38}-**H**), 1.34–1.23 (m, 14H, $C_{41–47}$-$\mathbf{H_2}$), 0.95–0.92 (m, *J* = 7.0, 6.9 Hz, 15H, five of –CH(C$\mathbf{H}_3$)), 0.88 (t, *J* = 7.0 Hz, 3H, C_{48}-$\mathbf{H_3}$), 0.81 (d, *J* = 7.0 Hz, 3H, one of –CH(C$\mathbf{H}_3$)), 0.74 (d, *J* = 6.9 Hz, 3H, one of –CH(C$\mathbf{H}_3$)); ^{13}C-NMR (125 MHz, CD_3OD) δ 140.5, 140.2, 140.0, 140.0, 139.5, 130.0, 129.4, 129.4, 129.3, 129.3, 129.2, 128.9, 128.8, 128.7, 128.5, 128.5, 128.4, 99.9, 84.6, 81.7, 81.5, 80.0, 78.9, 77.0, 76.7, 76.7, 76.1, 76.1, 75.9, 75.6, 74.7, 74.3, 74.0, 74.0, 74.0, 73.2, 72.5, 71.8, 71.8, 71.4, 70.7, 70.5, 69.8, 68.7, 45.5, 43.0, 43.0, 43.0, 42.6, 42.6, 42.1, 40.1, 40.0, 39.7, 39.2, 37.2, 36.7, 33.1, 32.1, 32.1, 31.0, 30.9, 30.9, 30.6, 28.7, 26.8, 23.8, 21.3, 18.9, 14.5, 13.7, 11.5, 9.5, 6.5, 6.2; HRMS (ESI-TOF) *m/z* calcd for $C_{88}H_{136}NaO_{22}$ $[M+Na]^+$: 1567.9415, found: 1567.9435.

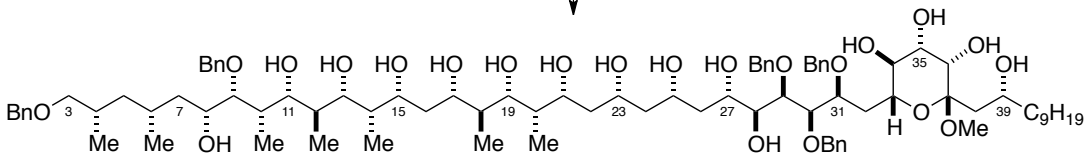


(2*S*,4*R*,6*R*,7*R*,8*S*,9*R*,10*R*,11*R*,12*S*,13*R*,15*S*,16*S*,17*R*,18*S*,19*R*,21*R*,23*S*,25*S*,26*S*,27*R*,28*R*,29*S*)-2,4,8,10,12,16,18-Heptamethyl-30-((2*R*,3*S*,4*S*,5*S*,6*S*)-3,4,5,6-tetrahydroxy-6-((*R*)-2-hydroxyundecyl)tetrahydro-2*H*-pyran-2-yl)triacontane-1,6,7,9,11,13,15,17,19,21,23,25,26,27,28,29-hexadecaol (1). To a solution of pentabenzyl ether **74** (12 mg, 7.7 μmol, 1.0 equiv) in 6:1 dioxane/H_2O (0.31 mL, 25 mM wrt **74**) at rt was added palladium black (~10 mg). The reaction mixture was purged with hydrogen for 1 min, stirred vigorously for 12 h, then recharged with additional catalyst at this time and

approximately every 12 h thrice after (total palladium black added: ~50 mg). The reaction mixture was stirred at rt for 20 h, then filtered through Celite®. The filter cake was rinsed with 1:1 THF/CH_3OH (15 mL total), and the filtrate concentrated. Reversed-phase C18 column chromatography (gradient elution, 5% → 100% CH_3CN in H_2O; eluted 50% → 70%) afforded aflastatin A C3–C48 degradation lactol **1** (4.5 mg, 53% yield) as a white solid. $[\alpha]_D^{25}$ +7.2° (*c* = 0.29, 3:1 CH_3OH/THF); IR (neat) 3319 (br), 2923, 2858, 1571, 1452, 1321, 1277, 1158, 1092, 973, 848 cm^{-1}; ^{1}H-NMR (600 MHz, C_5D_5N) δ 7.00 (d, *J* = 4.5 Hz, 1H, C_{35}-O**H**), 6.81 (d, *J* = 5.0 Hz, 1H, C_{34}-O**H**), 6.69 (d, *J* = 4.7 Hz, 1H, C_{27}-O**H**), 6.52 (d, *J* = 6.7 Hz, 1H, C_{27}-O**H**), 6.47 (br s, 1H, one of –O**H**), 6.43–6.39 (m, 2H, two of –O**H**), 6.35–6.31 (m, 2H, two of –O**H**), 6.30–6.21 (m, 5H, five of –O**H**), 6.10–6.05 (m, 3H, three of –O**H**), 5.98–5.92 (m, 3H, three of –O**H**), 5.87 (dd, *J* = 5.3, 5.3 Hz, 1H, C_3-O**H**), 5.03 (m, *J* = 5.4 Hz, 1H, C_{29}-**H**), 4.97 (m, *J* = 6.7 Hz, 1H, C_{31}-**H**), 4.85 (ddd, *J* = 9.8, 9.7, 2.9 Hz, 1H, C_{33}-**H**), 4.76 (dd, *J* = 9.4, 3.2 Hz, 1H, C_{35}-**H**), 4.72 (m, 1H, C_{39}-**H**), 4.68 (m, *J* = 8.8, 8.2 Hz, 1H, C_{27}-**H**), 4.62 (m, 1H, C_{25}-**H**), 4.61 (m, 1H, C_{17}-**H**), 4.58 (dd, *J* = 5.6, 1.8 Hz, 1H, C_{30}-**H**), 4.51–4.46 (m, 2H, C_{15}-**H** and C_{23}-**H**), 4.48 (d, *J* = 3.1 Hz, 1H, C_{36}-**H**), 4.43 (m, *J* = 8.8, 3.7 Hz, 1H, C_{21}-**H**), 4.38 (dd, *J* = 9.4, 9.4 Hz, 1H, C_{34}-**H**), 4.32 (m, 1H, C_{11}-**H**), 4.30 (m, 1H, C_{28}-**H**), 4.29 (m, 1H, C_8-**H**), 4.12 (m, *J* = 8.9 Hz, 1H, C_{13}-**H**), 4.06 (m, *J* = 9.7 Hz, 1H, C_{19}-**H**), 4.00 (dd, *J* = 4.7, 4.1 Hz, 1H, C_9-**H**), 3.80 (m, *J* = 10.4, 4.8 Hz, 1H, one of C_3-**H**), 3.61 (m, *J* = 10.4, 6.7 Hz, 1H, one of C_3-**H**), 3.21 (ddd, *J* = 13.6, 7.2, 2.8 Hz, 1H, one of C_{32}-**H**), 2.73 (m, *J* = 13.3 Hz, 1H, one of C_{38}-**H**), 2.60 (m, *J* = 12.9 Hz, 1H, one of C_{26}-**H**), 2.56 (ddd, *J* = 13.8, 10.1, 6.4 Hz, 1H, one of C_{32}-**H**), 2.31 (m, *J* = 6.4 Hz, 1H, C_{10}-**H**), 2.21 (m, *J* = 9.4, 6.7, 5.7 Hz, 1H, C_{18}-**H**), 2.16 (m, 1H, one of C_{26}-**H**), 2.15 (m, 1H, C_6-**H**), 2.14 (dd, *J* = 14.4, 10.6 Hz, 1H, one of C_{38}-**H**), 2.08 (m, 1H, C_{12}-**H**), 2.08–2.01 (m, 4H, one of C_{16}-**H**, one of C_{22}-**H**, and C_{24}-$\mathbf{H_2}$), 1.99 (m, 1H, C_4-**H**), 1.96 (m, 1H, one of C_{16}-**H**), 1.95 (m, 1H, C_{14}-**H**), 1.87 (m, 1H, C_{20}-**H**), 1.86 (m, 1H, one of C_{22}-**H**), 1.83 (m, *J* = 6.9, 5.4 Hz, 1H, one of C_7-**H**), 1.77 (m, *J* = 7.6, 6.0 Hz, 1H, one of C_5-**H**), 1.74 (m, *J* = 8.1, 5.9 Hz, 1H, one of C_7-**H**), 1.65 (m, 1H, one of C_{40}-**H**), 1.57–1.44 (m, 2H, one of C_{40}-**H**, and one of C_{41}-**H**), 1.35 (m, 1H, one of C_{41}-**H**), 1.31–1.10 (m, 10H, $C_{42–46}$-$\mathbf{H_2}$), 1.27 (d, *J* = 6.9 Hz, 3H, C_{51}-$\mathbf{H_3}$), 1.24 (d, *J* = 7.0 Hz, 3H, C_{53}-$\mathbf{H_3}$), 1.22 (m, 2H, C_{47}-$\mathbf{H_2}$), 1.20 (d, *J* = 7.0 Hz, 3H, C_{55}-$\mathbf{H_3}$), 1.10 (d, *J* = 6.7 Hz, 3H, C_{49}-$\mathbf{H_3}$), 1.06 (d, *J* = 6.6 Hz, 3H, C_{50}-$\mathbf{H_3}$), 1.05 (m, 1H, one of C_5-**H**), 0.97 (d, *J* = 6.9 Hz, 3H, C_{54}-$\mathbf{H_3}$), 0.83 (t, *J* = 7.1 Hz, 3H, C_{48}-$\mathbf{H_3}$), 0.80

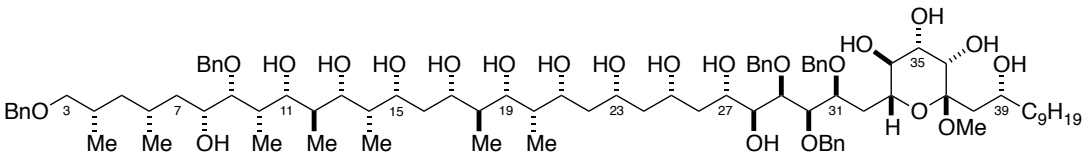
(d, J = 6.7 Hz, 3H, C_{52}-$\mathbf{H_3}$); ^{13}C-NMR (125 MHz, C_5D_5N) δ 100.1 (C37), 81.6 (C13), 78.9 (C11), 78.8 (C19), 78.0 (C9), 77.1 (C15), 76.3 (C21), 76.1 (C28), 75.1 (C36), 74.2 (C30), 74.0 (C17), 73.3 (C34), 72.9 (C35), 72.3 (C27), 71.7 (C33), 71.4 (C29), 71.3 (C25), 71.0 (C31), 70.7 (C23), 69.5 (C8), 69.0 (C39), 67.3 (C3), 45.7 (C16), 42.8 (C38), 42.7 (C18), 42.7 (C22), 42.4 (C7), 42.1 (C26), 41.6 (C5), 39.6 (C40), 39.5 (C20), 39.5 (C14), 38.8 (C12), 38.1 (C10), 37.4 (C32), 37.0 (C24), 34.0 (C4), 32.1 (C46), 30.1 (C44), 29.9 (C43), 29.8 (C42), 29.6 (C45), 27.9 (C6), 25.9 (C41), 22.9 (C47), 21.7 (C50), 18.7 (C49), 14.3 (C48), 13.2 (C52), 11.7 (C54), 8.3 (C51), 6.4 (C53), 6.1 (C55); HRMS (ESI-TOF) *m/z* calcd for $C_{53}H_{106}NaO_{22}$ $[M+Na]^+$: 1117.7068, found: 1117.7111.



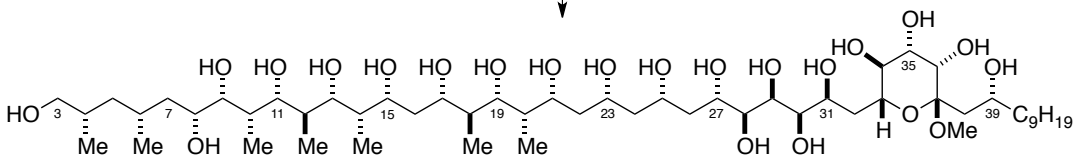


(2*S*,3*R*,4*R*,5*S*,6*S*,8*S*,10*R*,12*R*,13*S*,14*R*,15*S*,16*S*,18*R*,19*S*,20*R*,21*R*,22*R*,23*S*,24*R*,25*R*,27*R*,29*S*)-2,3,4,24,30-Pentakis(benzyloxy)-13,15,19,21,23,27,29-heptamethyl-1-((2*R*,3*S*,4*S*,5*S*,6*S*)-3,4,5-trihydroxy-6-((*R*)-2-hydroxyundecyl)-6-methoxytetrahydro-2*H*-pyran-2-yl)triacontan-5,6,8,10,12,14,16,18,20,22,25-undecaol (89). To a solution of lactol **74** (34 mg, 22 μmol, 1.0 equiv) in CH_3OH (1.1 mL, 20 mM wrt **74**) at rt was added Dowex® 50WX8 hydrogen form ion-exchange resin (0.22 g, 10 mg/μmol **74**, 200–400 mesh). The reaction mixture was stirred at 30 °C for 2 d, then filtered through Celite®. The filter cake was rinsed with 1:1 CH_2Cl_2/CH_3OH (15 mL total), and the filtrate concentrated. Pipette column chromatography (gradient elution, 4.5% → 5% → 6% CH_3OH in CH_2Cl_2) afforded lactol methyl ether **89** (0.013 g, 39% yield) as a clear, colorless oil. $[\alpha]_D^{25}$ +0.30° (c = 0.67, CH_3OH); IR (neat) 3379 (br), 3036, 2926, 2854, 1454, 1384, 1331, 1207, 1105, 1066, 976, 847, 735, 698 cm^{-1}; ^{1}H-NMR (600 MHz, CD_3OD) δ 7.43–7.21 (m, 25H, Ar**H**), 4.85 (d, J =

11.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.79 (d, *J* = 10.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.75 (d, *J* = 11.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.74 (d, *J* = 10.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.66 (d, *J* = 11.3 Hz, 1H, one of –OC**H**$_2$Ph), 4.60 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.55 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.49 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.45 (m, 2H, two of –OC**H**$_2$Ph), 4.25 (m, *J* = 7.9 Hz, 1H), 4.06 (m, *J* = 4.4, 4.1, 3.5 Hz, 1H), 4.02 (m, *J* = 4.8, 3.5 Hz, 1H), 4.01 (m, *J* = 2.6 Hz, 1H), 3.99–3.94 (m, *J* = 8.3, 6.9, 4.2 Hz, 3H), 3.97 (m, 1H, C_{31}-**H**), 3.91 (m, 1H), 3.90 (d, *J* = 3.7 Hz, 1H, C_{36}-**H**), 3.88–3.84 (m, *J* = 6.3, 2.5 Hz, 2H), 3.79 (m, *J* = 2.1 Hz, 1H), 3.78 (dd, *J* = 9.5, 3.7 Hz, 1H, C_{35}-**H**), 3.69 (m, *J* = 6.6, 1.8 Hz, 1H), 3.65 (m, *J* = 9.6, 1.8 Hz, 1H), 3.48 (dd, *J* = 9.5, 9.4 Hz, 1H, C_{34}-**H**), 3.42 (ddd, *J* = 9.2, 9.2, 2.2 Hz, 1H, C_{33}-**H**), 3.35 (m, *J* = 8.2, 1.4 Hz, 1H), 3.33 (dd, *J* = 9.2, 4.0 Hz, 1H, one of C_3-**H**), 3.31 (m, 1H), 3.23 (dd, *J* = 9.2, 6.6 Hz, 1H, one of C_3-**H**), 3.07 (s, 3H, –OC**H**$_3$), 2.57 (m, *J* = 12.1, 8.5 Hz, 1H, one of C_{32}-**H**), 2.25 (m, *J* = 7.0, 6.9, 6.7 Hz, 1H, C_{10}-**H**), 1.97 (ddd, *J* = 14.4, 4.7, 2.6 Hz, 1H), 1.93 (ddd, *J* = 14.1, 9.2, 3.7 Hz, 1H, one of C_{32}-**H**), 1.90–1.73 (m, 6H), 1.84 (m, 1H, one of C_4-**H**), 1.71–1.39 (m, 14H), 1.38–1.24 (m, 14H, $C_{41–47}$-**H**$_2$), 0.95–0.92 (m, *J* = 7.2 Hz, 15H, five of –CH(C**H**$_3$)), 0.89 (t, *J* = 7.0 Hz, 3H, C_{48}-**H**$_3$), 0.81 (d, *J* = 6.9 Hz, 3H, one of –CH(C**H**$_3$)), 0.74 (d, *J* = 6.7 Hz, 3H, one of –CH(C**H**$_3$)); ^{13}C-NMR (125 MHz, CD_3OD) δ 140.5, 140.1, 140.0, 140.0, 139.7, 129.7, 129.4, 129.3, 129.3, 129.3, 129.2, 129.2, 129.0, 128.7, 128.7, 128.6, 128.5, 128.5, 128.5, 103.4, 84.6, 82.1, 81.7, 80.2, 78.8, 77.0, 77.0, 76.7, 76.2, 76.0, 76.0, 75.6, 75.4, 74.3, 74.0, 74.0, 72.9, 72.5, 72.2, 72.1, 71.9, 71.8, 70.8, 70.5, 68.8, 68.1, 48.5, 45.3, 43.0, 43.0, 43.0, 42.6, 42.0, 40.2, 40.0, 39.7, 39.2, 39.0, 37.2, 36.8, 33.1, 32.4, 32.1, 30.8, 30.8, 30.7, 30.5, 28.7, 26.6, 23.7, 21.3, 18.9, 14.5, 13.7, 11.5, 9.5, 6.5, 6.2; HRMS (ESI-TOF) *m/z* calcd for $C_{89}H_{138}NaO_{22}$ $[M+Na]^+$: 1581.9572, found: 1581.9502.



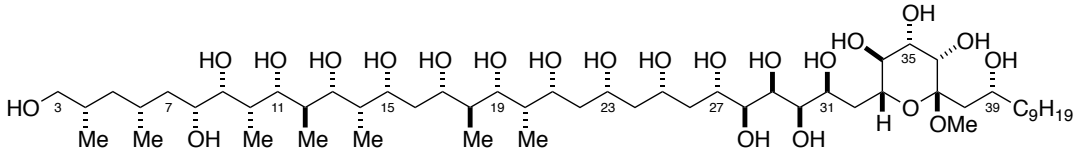
89



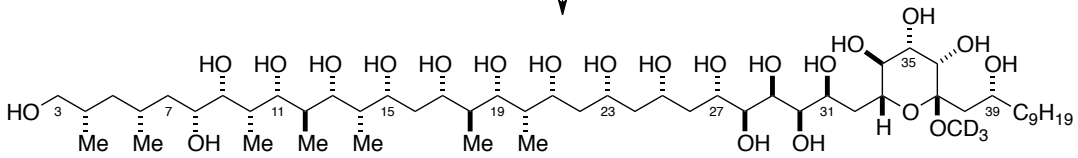
46a

(2*S*,4*R*,6*R*,7*R*,8*S*,9*R*,10*R*,11*R*,12*S*,13*R*,15*S*,16*S*,17*R*,18*S*,19*R*,21*R*,23*S*,25*S*,26*S*,27*R*,28*R*,29*S*)-2,4,8,10,12,16,18-Heptamethyl-30-((2*R*,3*S*,4*S*,5*S*,6*S*)-3,4,5-trihydroxy-6-((*R*)-2-hydroxyundecyl)-6-methoxytetrahydro-2*H*-pyran-2-yl)triacontane-1,6,7,9,11,13,15,17,19,21,23,25,26,27,28,29-hexadecaol (46a). To a solution of pentabenzyl ether **89** (13 mg, 8.3 μmol, 1.0 equiv) in 6:1 dioxane/H_2O (0.33 mL, 25 mM wrt **89**) at rt was added palladium black (~10 mg). The reaction mixture was purged with hydrogen for 1 min, stirred vigorously for 12 h, then recharged with additional catalyst at this time and approximately every 12 h thrice after (total palladium black added: ~50 mg). The reaction mixture was stirred at rt for 20 h, then filtered through Celite®. The filter cake was rinsed with 1:1 THF/CH_3OH (15 mL total), and the filtrate concentrated. Reversed-phase C18 column chromatography (gradient elution, 30% → 90% CH_3CN in H_2O; eluted 45% → 60%) afforded aflastatin A C3–C48 degradation lactol methyl ether **46a** (6.8 mg, 74% yield) as a white solid. $[\alpha]_D^{24}$ +14.0° (*c* = 0.65, CH_3OH); IR (neat) 3353 (br), 2925, 2858, 1444, 1382, 1318, 1209, 1108, 1034, 968, 848 cm^{-1}; ^{1}H-NMR (600 MHz, C_5D_5N) δ 6.89 (d, *J* = 3.5 Hz, 1H, one of –O**H**), 6.63 (d, *J* = 4.4 Hz, 1H, one of –O**H**), 6.49 (d, *J* = 3.5 Hz, 1H, C_{39}-O**H**), 6.46 (br s, 1H, one of –O**H**), 6.41 (br s, 1H, one of –O**H**), 6.38 (d, *J* = 4.7 Hz, 1H, one of –O**H**), 6.31–6.23 (m, 4H, four of –O**H**), 6.20 (d, *J* = 6.9 Hz, 1H, C_{35}-O**H**), 6.12 (d, *J* = 4.5 Hz, 1H, C_{31}-O**H**), 6.11–6.04 (m, 4H, four of –O**H**), 5.99 (d, *J* = 4.4 Hz, 1H, C_{29}-O**H**), 5.96–5.92 (m, 2H, two of –O**H**), 5.87 (dd, *J* = 5.3, 5.0 Hz, 1H, C_3-O**H**), 4.96 (m, *J* = 3.8 Hz, 1H, C_{29}-**H**), 4.93 (m, *J* = 2.3 Hz, 1H, C_{31}-**H**), 4.67 (d, *J* = 3.7 Hz, 1H, C_{36}-**H**), 4.67 (m, *J* = 3.2 Hz, 1H, C_{27}-**H**), 4.64 (m, 1H, C_{25}-**H**), 4.62 (m, *J* = 8.2 Hz, 1H, C_{17}-**H**), 4.56 (dd, *J* = 9.1, 3.5 Hz, 1H, C_{35}-**H**), 4.52–4.46 (m, *J* = 2.8 Hz, 3H, C_{15}-**H**, C_{23}-**H** and C_{30}-**H**), 4.42 (m, *J* = 6.7 Hz, 1H, C_{21}-**H**), 4.34 (m, *J* = 7.0 Hz, 1H, C_{28}-**H**), 4.32 (dd, *J* = 9.5, 9.4 Hz, 1H, C_{34}-**H**), 4.31 (m, *J* = 8.6 Hz, 1H, C_{11}-**H**), 4.28 (m, 1H, C_8-**H**), 4.23 (ddd, *J* = 9.3, 9.1, 2.5 Hz, 1H, C_{33}-**H**), 4.19 (m, *J* = 5.9, 5.7, 4.6 Hz, 1H, C_{39}-**H**), 4.12 (m, *J* = 8.5 Hz, 1H, C_{13}-**H**), 4.05 (m, *J* = 9.8 Hz, 1H, C_{19}-**H**), 4.00 (m, *J* = 4.4, 4.0 Hz, 1H, C_9-**H**), 3.80 (ddd, *J* = 10.2, 5.1, 4.6 Hz, 1H, one of C_3-**H**), 3.61 (ddd, *J* = 10.1, 6.7, 5.2 Hz, 1H, one of C_3-**H**), 3.35 (s, 3H, C_{56}-$\mathbf{H_3}$), 3.17 (ddd, *J* = 14.1, 6.4, 2.5 Hz, 1H, one of C_{32}-**H**), 2.60 (m, *J* = 14.1 Hz, 1H, one of C_{26}-**H**), 2.49 (ddd, *J* = 14.1, 8.5, 6.4 Hz, 1H, one of C_{32}-**H**), 2.45 (dd, *J* = 15.3, 9.3 Hz, 1H, one of C_{38}-**H**), 2.30 (m, *J* = 6.5 Hz, 1H, C_{10}-**H**), 2.21 (m, 1H, C_{18}-**H**), 2.20 (m, *J* = 14.9 Hz, 1H, one of C_{38}-**H**), 2.17 (m, 1H, one of C_{26}-**H**), 2.15 (m,

J = 6.9 Hz, 1H, C_6-**H**), 2.08 (m, 1H, C_{12}-**H**), 2.07–2.00 (m, 3H, one of C_{16}-**H**, one of C_{22}-**H**, and one of C_{24}-**H**), 2.00–1.92 (m, 4H, C_4-**H**, C_{14}-**H**, one of C_{16}-**H**, and one of C_{24}-**H**), 1.87 (m, 1H, C_{20}-**H**), 1.85 (m, 1H, one of C_{22}-**H**), 1.83 (m, J = 6.7, 5.1 Hz, 1H, one of C_7-**H**), 1.77 (m, J = 7.5, 6.3 Hz, 1H, one of C_5-**H**), 1.75 (m, J = 7.9, 6.0 Hz, 1H, one of C_7-**H**), 1.67 (m, 1H, one of C_{40}-**H**), 1.63–1.53 (m, 2H, one of C_{40}-**H**, and one of C_{41}-**H**), 1.47 (m, 1H, one of C_{41}-**H**), 1.32–1.14 (m, 10H, $C_{42–46}$-$\mathbf{H_2}$), 1.28 (d, J = 6.9 Hz, 3H, C_{51}-$\mathbf{H_3}$), 1.24 (d, J = 6.9 Hz, 3H, C_{53}-$\mathbf{H_3}$), 1.22 (m, 2H, C_{47}-$\mathbf{H_2}$), 1.19 (d, J = 6.9 Hz, 3H, C_{55}-$\mathbf{H_3}$), 1.10 (d, J = 6.7 Hz, 3H, C_{49}-$\mathbf{H_3}$), 1.06 (d, J = 6.7 Hz, 3H, C_{50}-$\mathbf{H_3}$), 1.04 (m, 1H, one of C_5-**H**), 0.97 (d, J = 6.7 Hz, 3H, C_{54}-$\mathbf{H_3}$), 0.83 (t, J = 7.0 Hz, 3H, C_{48}-$\mathbf{H_3}$), 0.80 (d, J = 6.9 Hz, 3H, C_{52}-$\mathbf{H_3}$); ^{13}C-NMR (125 MHz, C_5D_5N) δ 103.3 (C37), 81.6 (C13), 78.9 (C11), 78.9 (C19), 78.0 (C9), 77.1 (C15), 76.3 (C21), 76.3 (C28), 75.5 (C30), 74.0 (C17), 73.1 (C36), 72.8 (C33), 72.6 (C35), 72.4 (C34), 72.2 (C27), 71.5 (C29), 71.1 (C25), 70.9 (C31), 70.9 (C23), 69.5 (C8), 67.3 (C3), 66.9 (C39), 47.8 (C56), 45.8 (C16), 42.8 (C18), 42.8 (C22), 42.4 (C7), 42.1 (C26), 41.6 (C5), 39.5 (C20), 39.5 (C14), 39.4 (C38), 39.4 (C40), 38.8 (C12), 38.1 (C10), 37.6 (C32), 37.0 (C24), 34.0 (C4), 32.1 (C46), 30.0 (C44), 30.0 (C43), 29.8 (C42), 29.5 (C45), 27.9 (C6), 26.0 (C41), 22.9 (C47), 21.7 (C50), 18.7 (C49), 14.3 (C48), 13.2 (C52), 11.7 (C54), 8.3 (C51), 6.4 (C53), 6.1 (C55); HRMS (ESI-TOF) m/z calcd for $C_{54}H_{108}NaO_{22}$ $[M+Na]^+$: 1131.7225, found: 1131.7209.



46a



46b

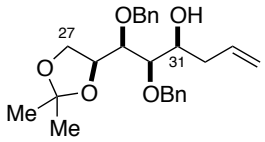
(2*S*,4*R*,6*R*,7*R*,8*S*,9*R*,10*R*,11*R*,12*S*,13*R*,15*S*,16*S*,17*R*,18*S*,19*R*,21*R*,23*S*,25*S*,26*S*,27*R*,28*R*,29*S*)-2,4,8,10,12,16,18-Heptamethyl-30-((2*R*,3*S*,4*S*,5*S*,6*S*)-3,4,5-trihydroxy-6-((*R*)-2-hydroxyundecyl)-6-($^2H_3$)methoxytetrahydro-2*H*-pyran-2-yl)triacontane-

1,6,7,9,11,13,15,17,19,21,23,25,26,27,28,29-hexadecaol (46b). To a solution of lactol methyl ether **46a** (6.8 mg, 6.1 μmol, 1.0 equiv) in CD_3OD (1.5 mL, 4.0 mM wrt **46a**) at rt was added Dowex® 50WX8 hydrogen form ion-exchange resin (~1 mg, 200–400 mesh). The reaction mixture stood at rt for 18 h, then was filtered through Celite®. The filter cake was rinsed with 1:1 CH_2Cl_2/CH_3OH (15 mL total), and the filtrate concentrated. Reversed-phase C18 column chromatography (gradient elution, 5% → 100% CH_3CN in H_2O; eluted 50% → 65%) afforded aflastatin A C3–C48 degradation lactol trideuteriomethyl ether **46b** (5.4 mg, 79% yield) as a white solid. $[\alpha]_D^{24}$ +12.6° (*c* = 0.34, CH_3OH); IR (neat) 3331 (br), 2922, 2857, 1457, 1437, 1314, 1159, 1107, 1061, 969, 848 cm^{-1}; ^{1}H-NMR (600 MHz, C_5D_5N) δ 6.90 (br s, 1H, one of –O**H**), 6.63 (br s, 1H, one of –O**H**), 6.49 (br s, 1H, one of –O**H**), 6.45 (br s, 1H, one of –O**H**), 6.41 (br s, 1H, one of –O**H**), 6.37 (br s, 1H, one of –O**H**), 6.30–6.21 (m, 4H, four of –O**H**), 6.19 (br s, 1H, one of –O**H**), 6.11 (br s, 1H, one of –O**H**), 6.10–6.02 (m, 4H, four of –O**H**), 5.96 (br s, 1H, one of –O**H**), 5.95–5.91 (m, 2H, two of –O**H**), 5.90 (br s, 1H, one of –O**H**), 4.97 (m, *J* = 2.5 Hz, 1H, C_{29}-**H**), 4.92 (m, *J* = 2.6 Hz, 1H, C_{31}-**H**), 4.67 (d, *J* = 3.7 Hz, 1H, C_{36}-**H**), 4.67 (m, 1H, C_{27}-**H**), 4.64 (m, *J* = 4.2, 3.7 Hz, 1H, C_{25}-**H**), 4.62 (m, *J* = 7.0 Hz, 1H, C_{17}-**H**), 4.57 (dd, *J* = 9.1, 3.5 Hz, 1H, C_{35}-**H**), 4.52–4.45 (m, 3H, C_{15}-**H**, C_{23}-**H** and C_{30}-**H**), 4.42 (m, *J* = 8.6 Hz, 1H, C_{21}-**H**), 4.34 (m, *J* = 8.3 Hz, 1H, C_{28}-**H**), 4.31 (dd, *J* = 9.2, 9.1 Hz, 1H, C_{34}-**H**), 4.31 (m, 1H, C_{11}-**H**), 4.28 (m, *J* = 4.1, 4.0 Hz, 1H, C_8-**H**), 4.23 (m, *J* = 10.8, 5.1 Hz, 1H, C_{33}-**H**), 4.18 (m, *J* = 10.7, 5.9 Hz, 1H, C_{39}-**H**), 4.11 (m, *J* = 8.7 Hz, 1H, C_{13}-**H**), 4.05 (m, *J* = 9.5 Hz, 1H, C_{19}-**H**), 4.00 (m, *J* = 4.4, 4.1 Hz, 1H, C_9-**H**), 3.79 (m, *J* = 10.3, 4.8 Hz, 1H, one of C_3-**H**), 3.60 (m, *J* = 10.4, 6.7 Hz, 1H, one of C_3-**H**), 3.17 (ddd, *J* = 11.4, 3.4, 2.8 Hz, 1H, one of C_{32}-**H**), 2.59 (m, *J* = 13.8 Hz, 1H, one of C_{26}-**H**), 2.49 (ddd, *J* = 14.0, 7.5, 6.4 Hz, 1H, one of C_{32}-**H**), 2.44 (dd, *J* = 15.2, 9.4 Hz, 1H, one of C_{38}-**H**), 2.30 (m, *J* = 6.1 Hz, 1H, C_{10}-**H**), 2.21 (m, 1H, C_{18}-**H**), 2.20 (m, *J* = 15.2 Hz, 1H, one of C_{38}-**H**), 2.16 (m, 1H, one of C_{26}-**H**), 2.14 (m, *J* = 7.2 Hz, 1H, C_6-**H**), 2.08 (m, 1H, C_{12}-**H**), 2.07–2.00 (m, 3H, one of C_{16}-**H**, one of C_{22}-**H**, and one of C_{24}-**H**), 2.00–1.92 (m, 4H, C_4-**H**, C_{14}-**H**, one of C_{16}-**H**, and one of C_{24}-**H**), 1.87 (m, 1H, C_{20}-**H**), 1.85 (m, 1H, one of C_{22}-**H**), 1.83 (m, *J* = 6.7, 5.4 Hz, 1H, one of C_7-**H**), 1.76 (m, *J* = 7.6, 6.0 Hz, 1H, one of C_5-**H**), 1.74 (m, *J* = 7.9, 7.2, 6.4 Hz, 1H, one of C_7-**H**), 1.67 (m, 1H, one of C_{40}-**H**), 1.62–1.53 (m, 2H, one of C_{40}-**H**, and one of C_{41}-**H**), 1.47 (m, 1H, one of C_{41}-**H**), 1.32–1.13 (m, 10H, $C_{42–46}$-$\mathbf{H_2}$), 1.28 (d, *J* = 7.0 Hz, 3H, C_{51}-$\mathbf{H_3}$), 1.23

(d, J = 6.7 Hz, 3H, C_{53}-$\mathbf{H_3}$), 1.22 (m, 2H, C_{47}-$\mathbf{H_2}$), 1.19 (d, J = 6.9 Hz, 3H, C_{55}-$\mathbf{H_3}$), 1.10 (d, J = 6.7 Hz, 3H, C_{49}-$\mathbf{H_3}$), 1.06 (d, J = 6.6 Hz, 3H, C_{50}-$\mathbf{H_3}$), 1.04 (m, 1H, one of C_5-**H**), 0.97 (d, J = 6.7 Hz, 3H, C_{54}-$\mathbf{H_3}$), 0.83 (t, J = 7.1 Hz, 3H, C_{48}-$\mathbf{H_3}$), 0.80 (d, J = 6.9 Hz, 3H, C_{52}-$\mathbf{H_3}$); ^{13}C-NMR (125 MHz, C_5D_5N) δ 103.2 (C37), 81.6 (C13), 78.8 (C11), 78.7 (C19), 77.9 (C9), 77.1 (C15), 76.2 (C21), 76.2 (C28), 75.4 (C30), 73.9 (C17), 73.0 (C36), 72.7 (C33), 72.6 (C35), 72.3 (C34), 72.2 (C27), 71.5 (C29), 71.1 (C25), 70.9 (C31), 70.8 (C23), 69.5 (C8), 67.2 (C3), 66.9 (C39), 45.7 (C16), 42.7 (C18), 42.7 (C22), 42.3 (C7), 42.1 (C26), 41.6 (C5), 39.5 (C20), 39.5 (C14), 39.3 (C38), 39.3 (C40), 38.8 (C12), 38.1 (C10), 37.5 (C32), 36.9 (C24), 34.0 (C4), 32.0 (C46), 30.0 (C44), 29.9 (C43), 29.8 (C42), 29.5 (C45), 27.8 (C6), 26.0 (C41), 22.9 (C47), 21.6 (C50), 18.6 (C49), 14.2 (C48), 13.2 (C52), 11.6 (C54), 8.3 (C51), 6.4 (C53), 6.1 (C55); HRMS (ESI-TOF) *m/z* calcd for $C_{54}H_{105}D_3NaO_{22}$ $[M+Na]^+$: 1134.7413, found: 1134.7407.

Stereochemical Proof by Mosher's Ester Analysis

Homoallylic alcohol 64



64

H	δ_S (ppm)	δ_R (ppm)	$\Delta\delta = \delta_S - \delta_R$	
$C(CH_3)_2$	1.42	1.39	+0.03	
	1.34	1.30	+0.04	
C_{27}-H_2	3.69	3.59	+0.10	
	3.58	3.53	+0.05	
C_{28}-H	4.29	4.11	+0.18	
C_{29}-H	3.42	3.29	+0.13	L_2
C_{30}-H	3.63	3.60	+0.03	
$PhCH_2O$	4.59	4.59	0.00	
	4.53	4.51	+0.02	
$PhCH_2O$	4.68	4.48	+0.20	
	4.65	4.45	+0.20	
C_{32}-H	2.57	2.61	–0.04	
	2.24	2.37	–0.13	
C_{33}-H	5.62	5.71	–0.09	L_3
C_{34}-H	5.00	5.07	–0.07	
	4.97	5.01	–0.04	

Chapter

4

Synthesis of Aflastatin A

I. Installation of the Tetramic Acid

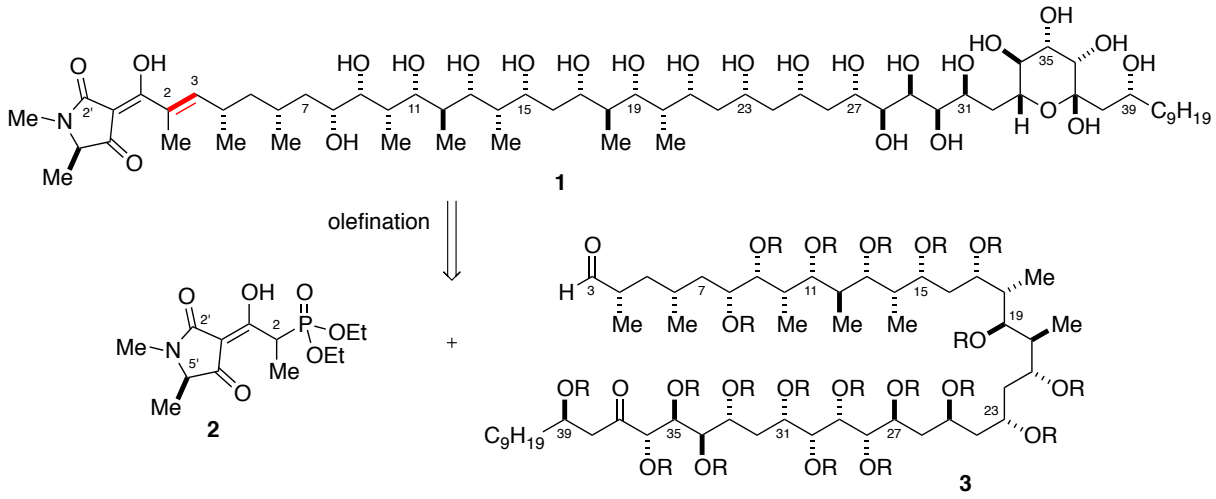
Our asymmetric syntheses of the aflastatin A (AsA) C3–C48 degradation fragments allowed us to confirm the stereochemical revision of AsA. Having achieved this objective, we finally turned our attention to the synthesis of the natural product itself. Unlike its C3–C48 degradation fragments, AsA is capped by a D-alanine-based tetramic acid moiety.[1] We therefore focused on developing a method for its installation.

Our first retrosynthesis plan for AsA (**1**) involved disconnection at C2–C3 to produce tetramic acid derivative **2** and C3–C48 aldehyde fragment **3** (Scheme 4.1).[2] We planned to install the tetramic acid by Wittig or Horner-Wadsworth-Emmons reaction as late in the synthesis as possible because we expected the C5' stereocenter to be readily epimerizable.[1b]

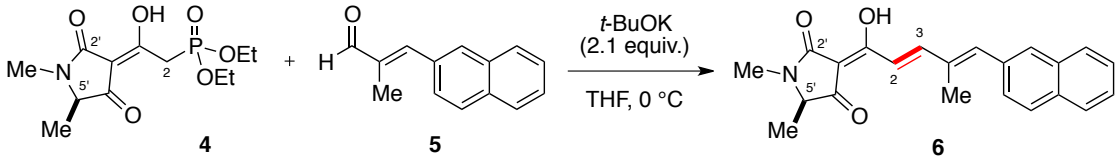
(1) For reviews of tetramic acid natural products, see: (a) Schobert, R.; Schlenk, A. *Bioorg. Med. Chem.* **2008**, *16*, 4203–4221; (b) Royles, B.J.L. *Chem. Rev.* **1995**, *95*, 1981–2001.

(2) Young, J.M. *Studies Toward the Synthesis of Aflastatin A*. Ph.D. Thesis, Harvard University, **2008**.

Scheme 4.1. Retrosynthesis plan for aflastatin A (**1**).



Precedent for this transformation was borne out of the syntheses of streptolydigin and the tirandamycins by the laboratories of Boeckman,[3] DeShong,[4] and Schlessinger.[5] In a separate yet closely related example, Rosen and coworkers made disubstituted (*E*) alkene **6** by addition of the potassium dianion of chiral tetramic acid phosphonate **4** to unsaturated aldehyde **5** (eq 1).[6] Fortunately, additions to aliphatic aldehydes under the same conditions were also known.[5a] However, the reaction of 2-methylated phosphonates such as **2** to produce trisubstituted (*E*) alkenes warranted investigation, so we embarked upon its synthesis.



(1)

(3) (a) Boeckman, R.K., Jr.; Thomas, A.J. *J. Org. Chem.* **1982**, *47*, 2823–2824; (b) Boeckman, R.K., Jr.; Starrett, J.E., Jr.; Nickell, D.G.; Sum, P.-E. *J. Am. Chem. Soc.* **1986**, *108*, 5549–5559; (c) Boeckman, R.K., Jr.; Potenza, J.C.; Enholm, E.J. *J. Org. Chem.* **1987**, *52*, 469–472.

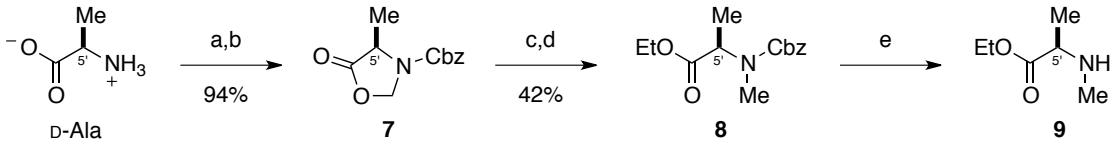
(4) (a) DeShong, P.; Ramesh, S.; Elango, V.; Perez, J.J. *J. Am. Chem. Soc.* **1985**, *107*, 5219–5224; (b) Shimshock, S.J.; Waltermire, R.E.; DeShong, P. *J. Am. Chem. Soc.* **1991**, *113*, 8791–8796.

(5) (a) Schlessinger, R.H.; Bebernitz, G.R. *J. Org. Chem.* **1985**, *50*, 1344–1346; (b) Schlessinger, R.H.; Bebernitz, G.R.; Lin, P. *J. Am. Chem. Soc.* **1985**, *107*, 1777–1778; (c) Schlessinger, R.H.; Graves, D.D. *Tetrahedron Lett.* **1987**, *28*, 4385–4388.

(6) Rosen, T.; Fernandes, P.B.; Marovich, M.A.; Shen, L.; Mao, J.; Pernet, A.G. *J. Med. Chem.* **1989**, *32*, 1062–1069.

The synthesis of tetramic acid phosphonate **2**[7] began with the preparation of *N*-methyl-D-alanine ethyl ester (**9**) in five steps from D-alanine (Scheme 4.2).[8] Reductive opening of oxazolidinone **7**[9] was followed by ethylation of the nascent carboxylate to produce *N*-methylated alanine derivative **8**. Deprotection provided *N*-methyl amino ester **9** as a dilute solution in dichloromethane for immediate use since it was prone to self-dimerization.

Scheme 4.2. Synthesis of *N*-methyl-D-alanine ethyl ester (**9**).



Reagents and conditions: (a) CbzCl, Na_2CO_3, dioxane, H_2O, 0 °C to rt; (b) $HO(CH_2O)_nH$, CSA, PhMe, 90 °C, 94% (2 steps); (c) Et_3SiH, TFA, CH_2Cl_2, 84%; (d) EtI, K_2CO_3, DMF, rt to 50 °C, 51%; (e) H_2, Pd/C, CH_2Cl_2, rt.

The synthesis of tetramic acid phosphonate **2** was then completed in five steps from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**10**) (Scheme 4.3).[2,8] Methylation, phosphination, and oxidative workup provided phosphonate **11**[10] in moderate overall yield. Cycloelimination of dioxinone **11** and capture of ethanethiol by the resultant acylketene intermediate[11] afforded β-ketothioester **12**[12] in excellent yield. Amide bond formation[13] and modified Lacey-Dieckmann cyclization[14] of β-ketoamide **13** produced tetramic acid phosphonate **2** in good overall yield.

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(7) The syntheses of tetramic acid phosphonate **2** and model tetramic acid **15** (*vide infra*) were performed as a collaboration between Dr. Joseph M. Young and David A. Thaisrivongs.

(8) Thaisrivongs, D.A. *Synthesis of the C5'–C2 and C36–C48 Subunits of Aflastatin A*. A.B. Thesis, Harvard University, **2007**.

(9) Aurelio, L.; Box, J.S.; Brownlee, R.T.C.; Hughes, A.B.; Sleebs, M.M. *J. Org. Chem.* **2003**, *68*, 2652–2667.

(10) (a) Boeckman, R.K., Jr.; Kamenecka, T.M.; Nelson, S.G.; Pruitt, J.R.; Barta, T.E. *Tetrahedron Lett.* **1991**, *32*, 2581–2584; (b) Boeckman, R.K., Jr.; Barta, T.E.; Nelson, S.G. *Tetrahedron Lett.* **1991**, *32*, 4091–4094; (c) Roush, W.R.; Brown, B.B. *J. Org. Chem.* **1993**, *58*, 2162–2172.

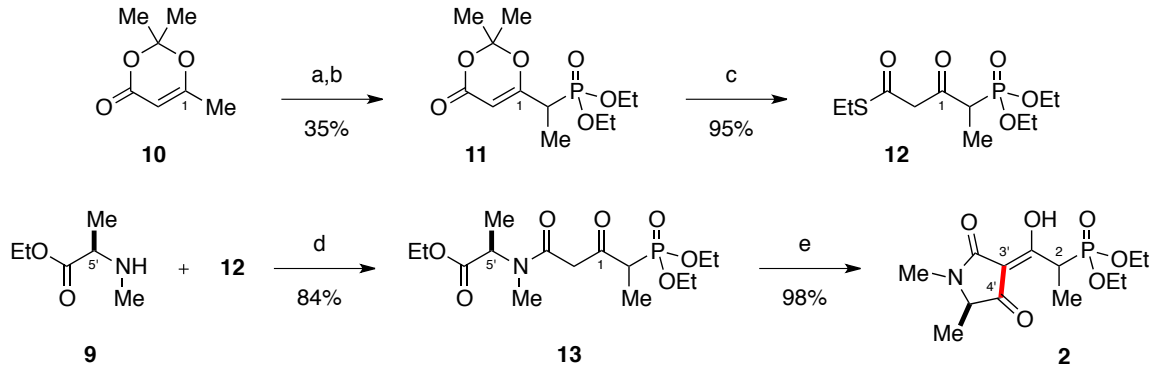
(11) (a) Clemens, R.J.; Hyatt, J.A. *J. Org. Chem.* **1985**, *50*, 2431–2435; (b) Sakaki, J.; Kobayashi, S.; Sato, M.; Kaneko, C. *Chem. Pharm. Bull.* **1990**, *38*, 2262–2264.

(12) (a) Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1998**, 313–314; (b) Hayashi, Y.; Kanayama, J.; Yamaguchi, J.; Shoji, M. *J. Org. Chem.* **2002**, *67*, 9443–9448.

(13) Kim, H.-O.; Olsen, R.K.; Choi, O.-S. *J. Org. Chem.* **1987**, *52*, 4531–4536.

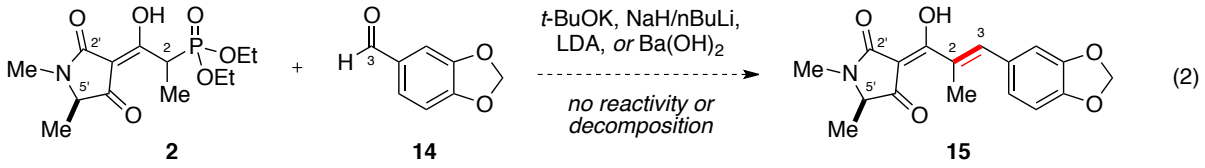
(14) (a) Lacey, R.N.; *J. Chem. Soc.* **1954**, 850–854; (b) Bloomer, J.L.; Kappler, F.E. *J. Chem. Soc., Perkin Trans. I* **1976**, 1485–1491.

Scheme 4.3. Synthesis of tetramic acid phosphonate **2**.



Reagents and conditions: (a) LDA, MeI, THF, –78 °C to 0 °C, 60%; (b) LiHMDS, $(EtO)_2PCl$, rt; aq H_2O_2, PhH, 0 °C, 59%; (c) EtSH, PhMe, 111 °C, 95%; (d) CuI, Et_3N, CH_2Cl_2, rt, 84% (2 steps from **8**); (e) Cs_2CO_3, THF, rt, 98%.

Our attempted addition of the potassium dianion of chiral tetramic acid phosphonate **2** to piperonal (**14**) resulted in decomposition (eq 2).[2,8] Several other bases were then screened (NaH/nBuLi, LDA, and $Ba(OH)_2$), but resulted in little to no reactivity, even at elevated temperatures. We attributed the lack of reactivity to the reduced kinetic acidity of phosphonate **2**. Deprotonation of the H2 proton is attenuated by minimization of allylic strain between the C2 stereocenter and tetramic acid ring.



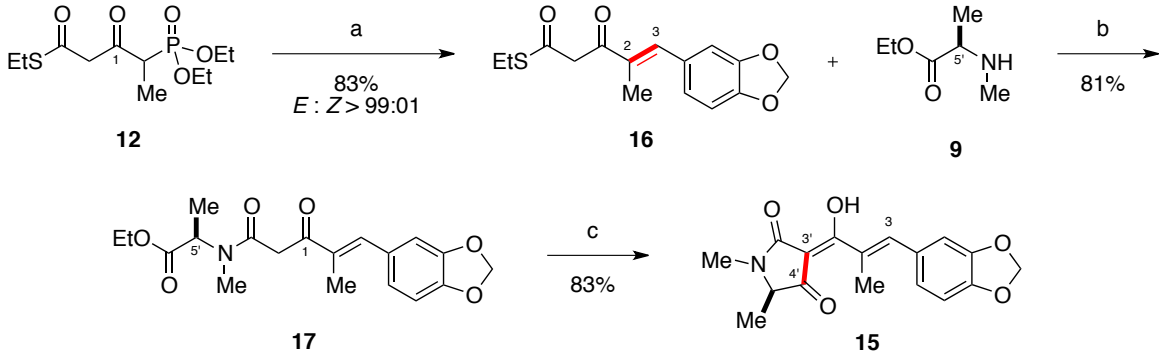
(2)

Although desirable, one-step installation of the tetramic acid was infeasible. As an alternative, Ley and coworkers reported a reliable three-step procedure for installing tetramic acids via olefination, amide bond formation, and cyclization.[15] Accordingly, addition of the sodium dianion of thioester phosphonate **12** to piperonal (**14**) produced the desired trisubstituted (*E*)-alkene **16** in very good yield and excellent *E*:*Z* selectivity (Scheme 4.4).

(15) (a) Ley, S.V.; Smith, S.C.; Woodward, P.R. *Tetrahedron Lett*. **1988**, *29*, 5829–5832; (b) Ley, S.V.; Smith, S.C.; Woodward, P.R. *Tetrahedron* **1992**, *48*, 1145–1174; (c) Burke, L.T.; Dixon, D.J.; Ley, S.V.; Rodríguez, F. *Org*. *Lett*. **2000**, *2*, 3611–3613.

Addition[13] of amine **9** to thioester **16** was followed by modified Lacey-Dieckmann cyclization[15b] of β-ketoamide **17** to complete the synthesis of model tetramic acid **15**[7] in good overall yield.

Scheme 4.4. Synthesis of model tetramic acid **15**.



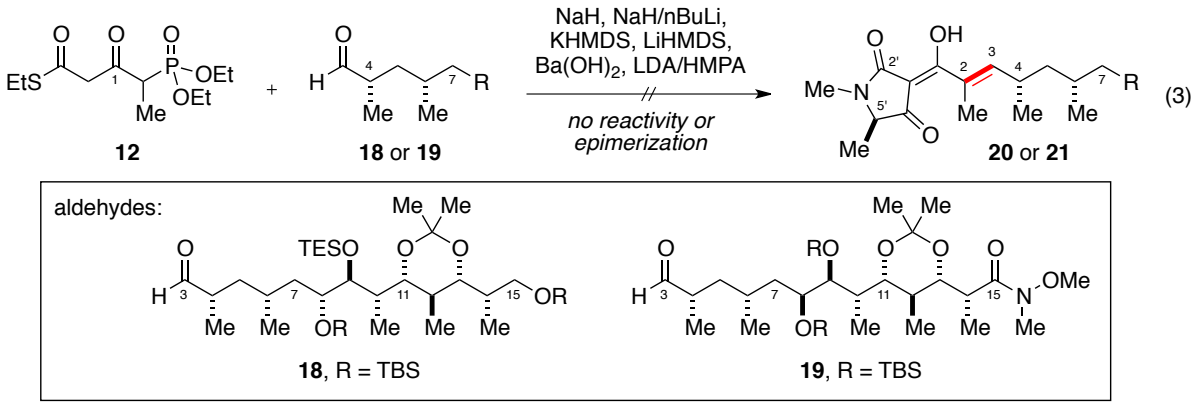
Reagents and conditions: (a) piperonal (**14**), NaH, THF, 0 °C to rt, 83%, *E* : *Z* > 99:01; (b) CuI, Et_3N, CH_2Cl_2, rt, 81%; (c) nBu_4NF, THF, rt, 83%.

We then attempted to subject more elaborate model aldehydes **18** and **19**[16] to this reaction sequence.[17] Unfortunately, addition of various metal dianions of thioester phosphonate **12** to these aldehydes resulted in epimerization of the C4 methyl stereocenter (eq 3). Throughout our screen of strong bases, aldehyde epimerization was accompanied by variable levels of conversion and *E*:*Z* selectivity. Although mild deprotonation of phosphonate **12** by $Ba(OH)_2$[18] curtailed epimerization, we only observed trace amounts of desired product. From these experiments we determined that phosphonates requiring double deprotonation for reactivity were incompatible with aldehydes bearing epimerizable α-stereocenters, and therefore would not be appropriate for our synthesis of AsA.

(16) Precursors to model aldehydes **18** and **19** were previously synthesized by Dr. Joseph M. Young. See: Ref. 2.

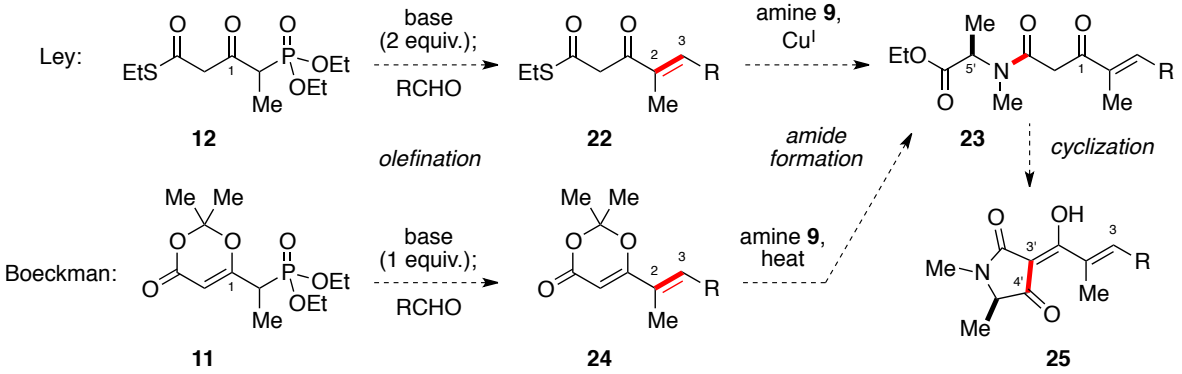
(17) Application of the Ley protocol to model aldehydes **18** and **19** was attempted by the author in collaboration with Dr. Egmont Kattnig.

(18) (a) Alvarez Ibarra, C.; Arias, S.; Fernández, M.J.; Sinisterra, J.V. *J. Chem. Soc., Perkin Trans. II* **1989**, 503–508; (b) Paterson, I.; Yeung, K.-S.; Smaill, J.B. *Synlett* **1993**, 774–776.



Ultimately, we found recourse in a three-step procedure developed by Boeckman, Jones and their respective coworkers.[19] Although the overall transformations are similar to Ley's protocol[15] (Scheme 4.5), olefination occurs under milder conditions and requires single deprotonation of dioxenone phosphonate **11**.[10b,20] Subsequently, amide formation occurs not by addition of an amine to a thioester, but rather by cycloelimination of dioxinone **24** and capture of amine **9** by the resultant acylketene intermediate to produce common β-ketoamide **23**.[21] Both strategies then generate the highly polar and readily epimerizable tetramic acid **25** in a final cyclization step.

Scheme 4.5. Ley and Boeckman procedures for tetramic acid installation.



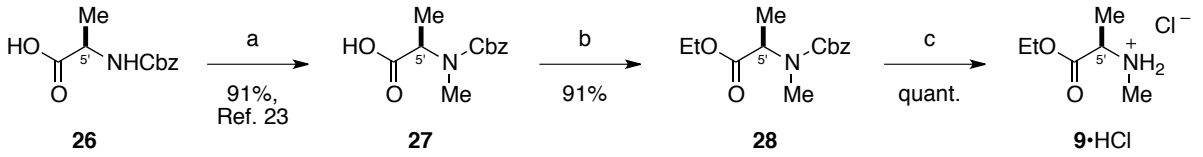
(19) (a) Boeckman, R.K., Jr.; Weidner, C.H.; Perni, R.B.; Napier, J.J. *J. Am. Chem. Soc.* **1989**, *111*, 8036–8037; (b) Jones, R.C.F.; Tankard, M. *J. Chem. Soc., Perkin Trans. I* **1991**, 240–241.

(20) (a) Boeckman, R.K., Jr.; Shao, P.; Wrobleski, S.T.; Boehmler, D.J.; Heintzelman, G.R.; Barbosa, A.J. *J. Am. Chem. Soc.* **2006**, *128*, 10572–10588; (b) Yoshinari, T.; Ohmori, K.; Schrems, M.G.; Pfaltz, A.; Suzuki, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 881–885.

(21) Sato, M.; Ogasawara, H.; Komatsu, S.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 3848–3856.

For the cycloelimination step, Jones and Tankard demonstrated that the reactant amino esters could be generated *in situ* from their corresponding hydrochloride salts.[19b] As such, we took this opportunity to synthesize a more stable form of amino ester **9**, namely its hydrochloride salt **9**•HCl,[22] in three steps from *N*-Cbz-D-alanine (**26**) (Scheme 4.6). Methylation,[23] ethyl ester formation,[8] and reductive removal of the Cbz protecting group under anhydrous acidic conditions produced the hydrochloride salt of *N*-methyl-D-alanine ethyl ester (**9**•HCl) in excellent overall yield.

Scheme 4.6. Synthesis of *N*-Me-D-Ala-OEt•HCl (**9**•HCl).



26 **27** **28** **9**•HCl

Reagents and conditions: (a) MeI, NaH, THF, 0 °C to rt, 91%, Ref. 23a; (b) EtI, K_2CO_3, DMF, 0 °C to rt, 91%; (e) H_2, Pd/C, AcCl, EtOH, rt, quant.

With both dioxinone phosphonate **11** (Scheme 4.3) and ammonium salt **9**•HCl in hand, we applied Boeckman's protocol[19] to the synthesis of model tetramic acid **32** (Scheme 4.7).[24] Addition of the lithium anion of phosphonate **11** to model aldehyde **19** in the presence of HMPA[10b,20] produced trisubstituted (*E*)-alkene **29** as a single isomer in excellent yield and without epimerization of the C4 methyl stereocenter. Next, cycloelimination[19b] of dioxinone **29** in the presence of ammonium salt **9**•HCl and molecular sieves (and the absence of exogenous base) led to the formation of β-ketoamide **30** in very good yield. Then, Lacey-Dieckmann cyclization[14] was induced by potassium trimethylsilanolate, rather than potassium

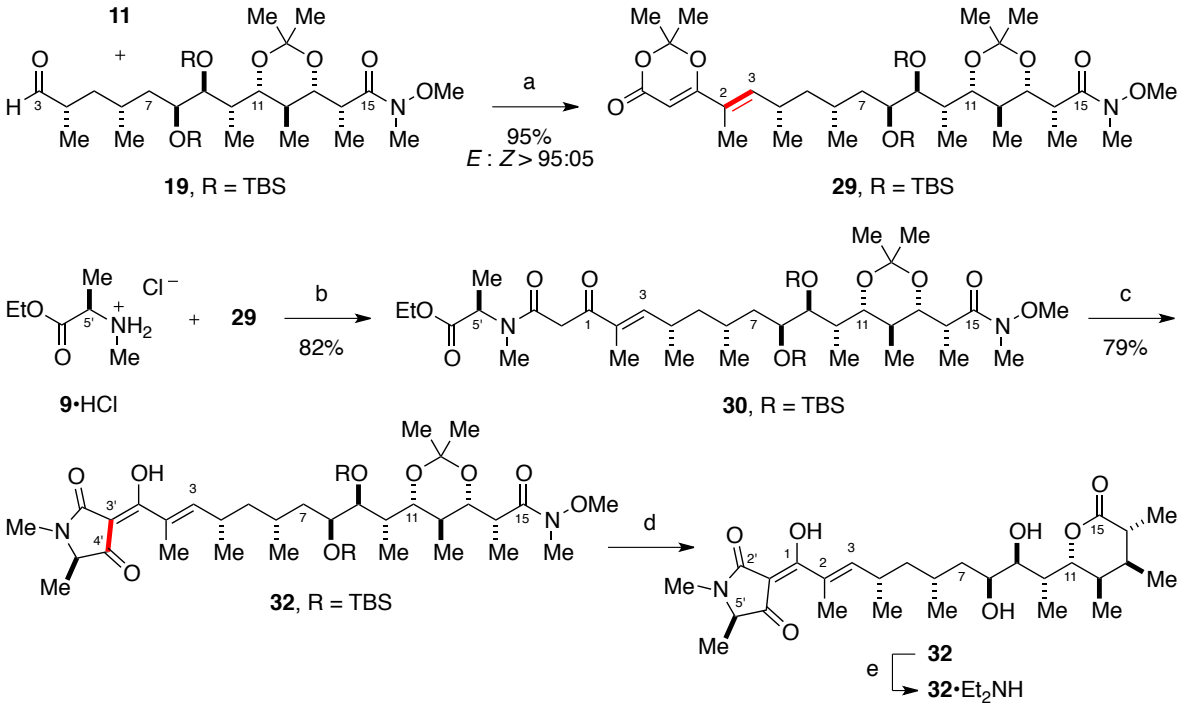
(22) The synthesis of the corresponding methyl ester was achieved by Dr. Egmont Kattnig. The synthesis of ammonium salt **9**•HCl represents the culminative work of David A. Thaisrivongs, Dr. Peter H. Fuller, and the author.

(23) (a) Trouche, N.; Wieckowski, S.; Sun, W.; Chaloin, O.; Hoebeke, J.; Fournel, S.; Guichard, G. *J. Am. Chem. Soc.* **2007**, *129*, 13480–13492; (b) Stodulski, M.; Mlynarski, J. *Tetrahedron: Asymmetry* **2008**, *19*, 970–975.

(24) The synthesis of tetramic acid **31** was first performed by Dr. Egmont Kattnig, and then modified by Dr. Peter H. Fuller. The synthesis of tetramate salt **32**•Et_2NH was performed in collaboration with Dr. Fuller.

tert-butoxide,[14b] to cleanly produce tetramic acid **31** in good yield. As before, removal of the acetonide and silyl protecting groups was achieved with hexafluorosilicic acid,[25] proceeded with concomitant lactonization, and ultimately furnished model 3-acyltetramic acid **32**. Importantly, both the cyclization and deprotection steps proceeded without appreciable epimerization of the C5' stereocenter.

Scheme 4.7. Synthesis of model tetramic acid **32**.



Reagents and conditions: (a) phosphonate **11**, LDA, THF, –78 °C to 0 °C; HMPA, –78 °C; aldehyde **19**, –78 °C to rt, 95%, *E*:*Z* > 95:05; (b) 4 Å MS, PhMe, 110 °C, 82%; (c) KOTMS, TMSOH, THF, 0 °C, 79%; (d) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt; (e) Et_2NH, MeOH, rt.

After completing the synthesis of model tetramic acid **32**, we compared its NMR spectroscopic data to that reported by the isolation group for AsA.[26] Acknowledging the obvious stereochemical and structural differences in the C8–C9 diol and C10–C15

(25) (a) Pilcher, A.S.; Hill, D.K.; Shimshock, S.J.; Waltermire, R.E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492–2495; (b) Pilcher, A.S.; Shimshock, S.J. *J. Org. Chem.* **1993**, *58*, 5130–5134.

(26) (a) Sakuda, S.; Ono, M.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Am. Chem. Soc.* **1996**, *118*, 7855–7856; (b) Ono, M.; Sakuda, S.; Suzuki, A.; Isogai, A. *J. Antibiotics* **1997**, *50*, 111–118; (c) Ono, M.; Suzuki, A.; Isogai, A.; Sakuda, S. Production Aflastatin A from *Streptomyces* sp., A Pharmaceutical Composition and Methods of Use. U.S. Patent 5,773,263, June 30, 1998.

polypropionate regions, respectively, we were still disappointed by the general disagreement of data sets in the seemingly removed N1'–C6'/C1–C3 enoyltetramate region. Additionally, we observed significant line broadening of resonances in the carbon NMR spectrum of model tetramic acid **32** due to rotameric and tautomeric equilibria.[27] At this point in time we realized that the isolation group purified AsA under basic conditions, and reported spectral data corresponding not to the free tetramic acid but its corresponding diethylamine salt.[26b,c] Unfortunately, conversion of model tetramic acid **32** to diethylammonium tetramate **32**•Et_2NH did not completely resolve chemical shift discrepancies in the C1–C3 enoyl region.

To resolve this issue, we undertook the synthesis of AsA tetramic acid degradation fragment **38** (Scheme 4.8).[28] Parikh-Doering oxidation[29] of C3 carbinol **33**[30] and reaction[10b,20] of resultant aldehyde **34** with dioxinone phosphonate **11** provided trisubstituted (*E*)-alkene **35** as a single isomer in good yield over two steps. Cycloelimination[19b] of dioxinone **35** in the presence of ammonium salt **9**•HCl led to the formation of β-ketoamide **36** in excellent yield. Modified Lacey-Dieckmann cyclization[14] was followed by silyl group removal[25] to furnish degradation fragment **38**. The free tetramic acid was then converted to its corresponding diethylamine salt **38**•Et_2NH.

Comparison of our NMR spectroscopic data for diethylammonium tetramate **38**•Et_2NH to that reported by the isolation group for the naturally derived tetramic acid

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(27) (a) Yamaguchi, T.; Saito, K.; Tsujimoto, T.; Yuki, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1161–1162; (b) Saito, K.; Yamaguchi, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 651–652; (c) Saito, K.; Yamaguchi, T. *J. Chem. Soc., Perkin Trans. II* **1979**, 1605–1609; (d) Steyn, P.S.; Wessels, P.L. *Tetrahedron Lett.* **1978**, *19*, 4707–4710; (d) Nolte, M.J.; Steyn, P.S.; Wessels, P.L. *J. Chem. Soc., Perkin Trans. I* **1980**, 1057–1065; (e) Steyn, P.S.; Wessels, P.L. *S. Afr. J. Chem.* **1980**, *33*, 120; (f) Jeong, Y.-C.; Moloney, M.G. *J. Org. Chem.* **2011**, *76*, 1342–1354 and references therein.

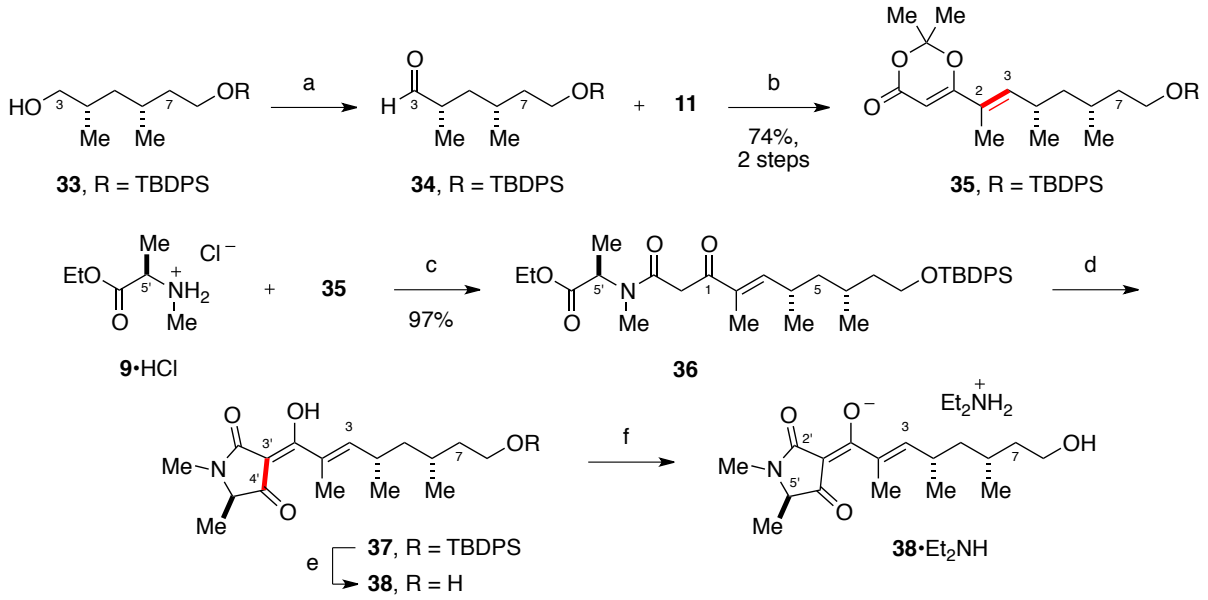
(28) The synthesis of degradation fragment **38**•Et_2NH was performed by the author.

(29) Parikh, J.R.; Doering, W.v.E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

(30) A precursor to carbinol **33** was previously synthesized by Dr. Joseph M. Young. See: Ch. 2.

degradation fragment **38**[26a,b] revealed a spectroscopic match save those resonances corresponding to the diethylammonium cation. Since naturally derived degradation fragment **38** was also purified under basic conditions, we concluded that the data tabulated by the isolation group for naturally derived AsA tetramic acid degradation fragment **38** should in fact be attributed to its derivative diethylammonium tetramate salt **38**•Et_2NH.

Scheme 4.8. Synthesis of degradation fragments **38** and **38**•Et_2NH.



Reagents and conditions: (a) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C; (b) phosphonate **11**, LDA, THF, –78 °C to 0 °C; HMPA, –78 °C; aldehyde **34**, –78 °C to rt, *E*:*Z* > 95:05. 74% (2 steps); (c) 4 Å MS, PhMe, 110 °C, 97%; (d) KOTMS, TMSOH, THF, 0 °C; (e) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt; (f) Et_2NH, MeOH, rt.

In the end, our synthesis of tetramate **38**•Et_2NH and its spectroscopic match to naturally derived tetramic acid degradation fragment **38** confirmed the absolute stereochemical assignment of the C5' stereocenter.[31] When taken together with our syntheses of the AsA C3–C48 degradation fragments, we confirmed both the revised stereochemical assignment and full absolute configuration of AsA.[32]

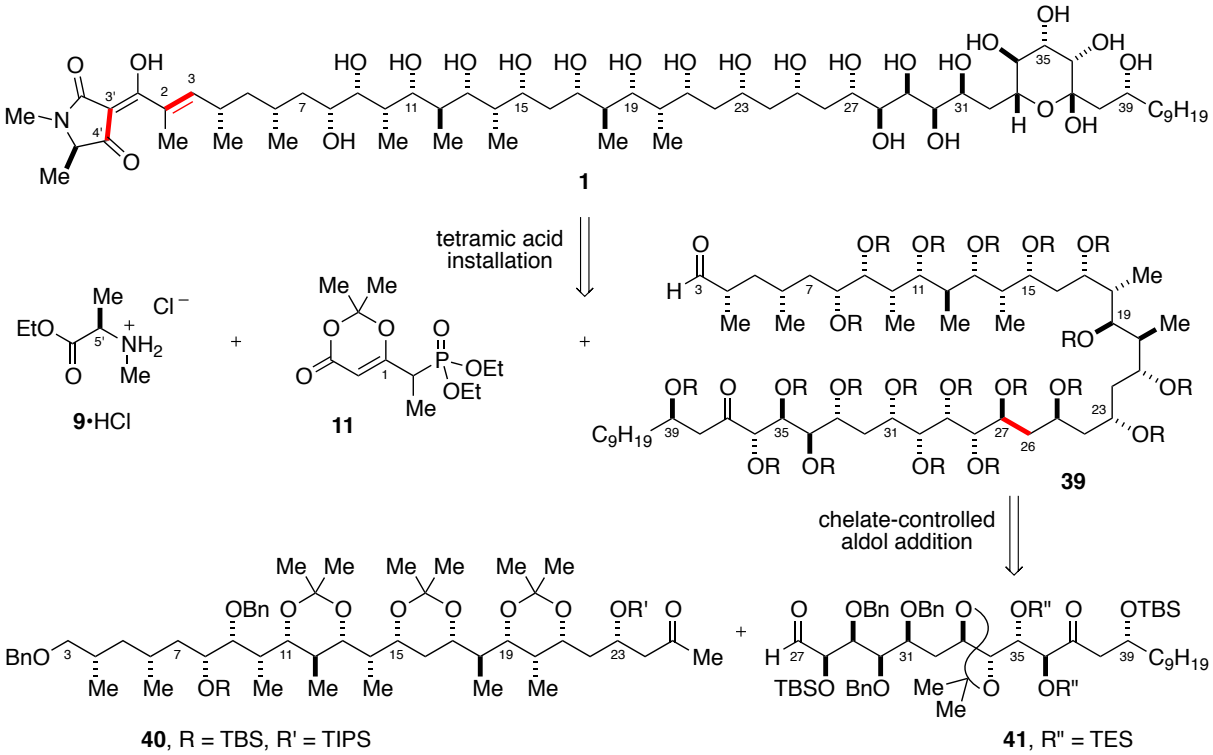
(31) Ikeda, H.; Matsumori, N.; Ono, M.; Suzuki, A.; Isogai, A.; Nagasawa, H.; Sakuda, S. *J. Org. Chem.* **2000**, *65*, 438–444.

(32) Sakuda, S.; Matsumori, N.; Furihata, K.; Nagasawa, H. *Tetrahedron Lett.* **2007**, *48*, 2527–2531.

II. Revised Synthesis of the C27–C48 Aldehyde

Having found a suitable method for installing the tetramic acid moiety, we embarked upon the synthesis of AsA (**1**) and its diethylamine salt. Our final retrosynthesis plan[33] for AsA (**1**) involved disconnections at C2–C3 and C3'–C4' to produce C3–C48 aldehyde **39**, as well as two tetramic acid precursors: the hydrochloride salt of *N*-methyl-D-alanine ethyl ester (**9**•HCl), and dioxinone phosphonate **11** (Scheme 4.9). In turn, we envisioned aldehyde **39** to arise from the diastereoselective aldol addition of C3–C26 ketone **40** to C27–C48 aldehyde **41**.[33] We took this opportunity to revise the original synthesis of C27–C48 aldehyde **41** in order to reduce the number of protecting group manipulation steps.[34]

Scheme 4.9. Retrosynthesis plan for aflastatin A (**1**).



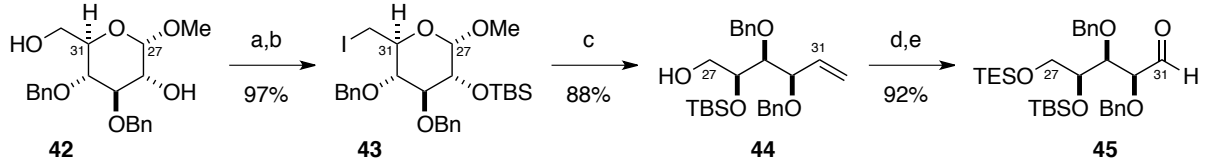
Our synthesis of C27–C48 aldehyde **41** began with the preparation of C27–C31

(33) Kattnig, E. *An Aldol Approach Toward Aflastatin A – Synthesis of the C3–C48 Polyol*. Postdoctoral Report, Harvard University, **2011**.

(34) The revised synthesis of C27–C48 aldehyde **41** was performed by the author.

aldehyde **46** from dibenzylglucopyranoside **42**[35] in five steps (Scheme 4.10). Iodination[36] and silylation produced pyranoside **43** in excellent overall yield. Zinc-mediated fragmentation[37] and *in situ* reduction produced enol **44**, which in turn was silylated and oxidatively cleaved, ultimately furnishing C27–C31 aldehyde **45** in 86% overall yield.

Scheme 4.10. Synthesis of C27–C31 aldehyde **45**.



42 **43** **44** **45**

Reagents and conditions: (a) PPh_3, I_2, imidazole, PhMe, MeCN, rt, 97%; (b) TBSCl, imidazole, CH_2Cl_2, 0 °C to rt, quant.; (c) Zn, THF, H_2O,))), 45 °C; $NaBH_4$, 0 °C, 88%; (d) TESCl, imidazole, CH_2Cl_2, 0 °C to rt, 98%; (e) O_3, py, CH_2Cl_2, MeOH, –78 °C; PPh_3, –78 °C to rt, 94%.

Our synthesis of C27–C48 aldehyde **41** continued with the stereoselective allylation of syn α,β-bisalkoxy aldehyde **45** (Scheme 4.11). Although both α- and β-oxygen substituents were available for chelation,[38] the rate of reaction of allylmagnesium bromide with the five-membered chelate[39] was significantly faster,[40] producing homoallylic alcohol **46** in 95% yield as a single diastereomer (d.r. ≥ 95:05). Acryloylation[41] of the nascent C31 carbinol, and ring-

(35) Français, A.; Urban, D.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8662–8665.

(36) (a) Garegg, P.J.; Samuellson, B. *J. Chem. Soc., Perkin Trans. I.* **1980**, 2866–2869; (b) Garegg, P.J.; Johansson, R.; Ortega, C.; Samuellson, B. *J. Chem. Soc., Perkin Trans. I.* **1982**, 681–683.

(37) Skaanderup, P.R.; Hyldtoft, L.; Madsen, R. *Monatsh. Chem.* **2002**, *133*, 467–472.

(38) The possibility of bicyclic chelates involving the aldehyde carbonyl and both oxygen substituents cannot be ruled out. See: (a) Charette, A.B.; Mellon C.; Rouillard, L.; Malenfant, E. *Pure Appl. Chem.* **1992**, *64*, 1925–1931; (b) Charette, A.B.; Mellon C.; Rouillard, L.; Malenfant, E. *Synlett* **1993**, 81–82.

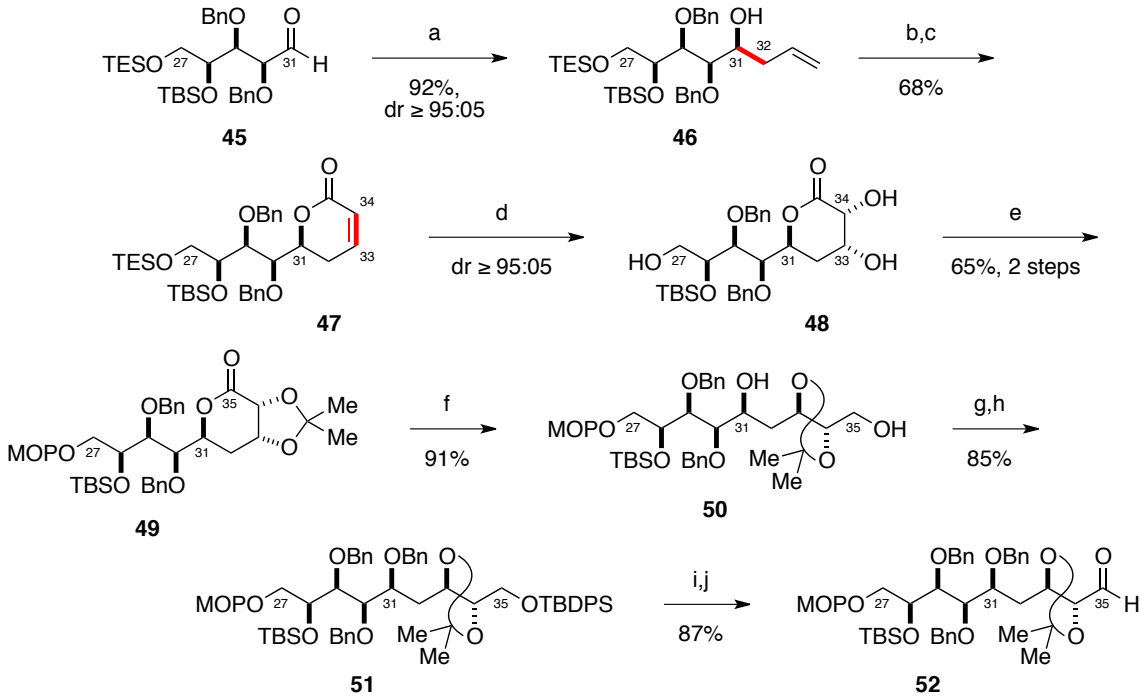
(39) (a) Cram, D.J.; Abd Elhafez, F.A. *J. Am. Chem. Soc.* **1952**, *74*, 5828–5835; (b) Cram, D.J.; Kopecky, K.R. *J. Am. Chem. Soc.* **1959**, *81*, 2748–2755; (c) Cram, D.J.; Leitereg, T.H. *J. Am. Chem. Soc.* **1968**, *90*, 4019–4026.

(40) For examples that suggest five-membered magnesium chelates react much faster than six-membered chelates, see: (a) Frye, S.V.; Eliel, E.L.; Cloux, R. *J. Am. Chem. Soc.* **1987**, *109*, 1862–1863; (b) Williams, D.R.; Klingler, F.D. *Tetrahedron Lett.* **1987**, *28*, 869–872; (c) Keck, G.E.; Andrus, M.B.; Romer, D.R. *J. Org. Chem.* **1991**, *56*, 417–420; (d) Burgess, K.; Chaplin, D.A. *Tetrahedron Lett.* **1992**, *33*, 6077–6080.

(41) Tanaka, A.; Suzuki, H.; Yamashita, K. *Agric. Biol. Chem.* **1989**, *53*, 2253–2256.

closing metathesis[42] of the intermediate diene then furnished unsaturated lactone **47**.

Scheme 4.11. Synthesis of C27–C35 aldehyde **52**.



Reagents and conditions: (a) $MgBr_2•OEt_2$, allylMgBr, CH_2Cl_2, Et_2O, PhMe, –78 °C, 92%, dr ≥ 95:05; (b) acrylic pivalic anhydride, $EtN(iPr)_2$, DMAP, THF, PhH, rt, 98%; (c) $(Ph_3P)_2Cl_2Ru$=CHPh, PhH, 65 °C, 69%; (d) $RuCl_3$, $CeCl_3•7H_2O$, $NaIO_4$, EtOAc, MeCN, H_2O, 0 °C, dr ≥ 95:05; (e) $Me_2C(OMe)_2$, PPTS, acetone, 35 °C, 65% (2 steps); (f) $LiBH_4$, H_2O, THF, 0 °C to rt, 91%; (g) TBDPSCl, imidazole, DMF, 0 °C, 92%; (h) BnBr, NaH, nBu_4NI, DMF, –20 °C to –5 °C, 92%; (i) nBu_4NF, AcOH, THF, rt, 93%; (j) $SO_3•Py$, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C, 94%.

Stereoselective dihydroxylation[43,44] proceeded with concomitant removal of the primary TES ether to give triol **48** as a single diastereomer. Acetonide formation and protection of the C27 carbinol as its 2-methoxy-2-propyl (MOP) ether[45] produced lactone **49** in good yield over two steps. Reduction to diol **50**, selective protection of the primary carbinol,

(42) Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R.H. *Angew. Chem.* **1995**, *107*, 2179–2181; *Angew. Chem., Int. Ed.* **1995**, *34*, 2039–2041.

(43) (a) Plietker, B.; Niggemann, M. *J. Org. Chem.* **2005**, *70*, 2402–2405; (b) Plietker, B. *Synthesis* **2005**, 2453–2472.

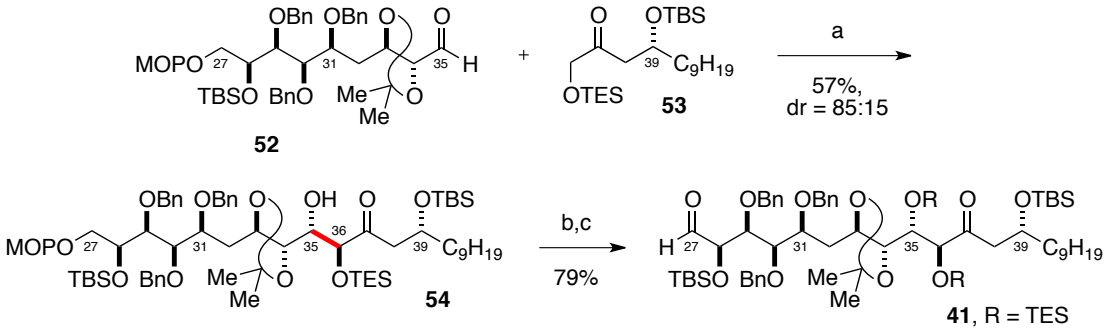
(44) For examples of the diastereoselective dihydroxylation of related α,β-unsaturated δ-lactones using Upjohn conditions (OsO_4, NMO), see: (a) Ghosh, A.K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 3967–3969; (b) Ramachandran, P.V.; Prabhudas, B.; Chandra, J.S.; Reddy, M.V.R. *J. Org. Chem.* **2004**, *69*, 6294–6304; (c) Bhaket, P.; Stauffer, C.S.; Datta, A. *J. Org. Chem.* **2004**, *69*, 8594–8601.

(45) For one of the earliest examples of using a 2-methoxy-2-propyl (MOP) ether as a carbinol protecting group, see: Kluge, A.F.; Untch, K.G.; Fried, J.H. *J. Am. Chem. Soc.* **1972**, *94*, 7827–7832.

and benzylation yielded disilyl ether **51**. Selective removal of the TBDPS ether and oxidation[29] of the resultant carbinol ultimately provided C27–C35 aldehyde **52** in 10 steps and 32% overall yield from aldehyde **45**.

With a more efficient route to aldehyde **52** in hand, the synthesis of the C27–C48 fragment **41** was nearly complete. Addition[46] of the corresponding (*E*) enolate of ketone **53** to aldehyde **52** produced the desired anti-Felkin product **54** in moderate yield and good diastereoselection (Scheme 4.12). Silylation of the C35 carbinol and selective cleavage of the primary MOP ether were then accomplished in one pot. Oxidation[29] of the resultant C27 carbinol completed the synthesis of C27–C48 aldehyde **41** in good overall yield and 21 linear steps from methyl α-D-(+)-glucopyranoside.

Scheme 4.12. Synthesis of C27–C48 aldehyde **41**.



Reagents and conditions: (a) ketone **53**, Cy_2BCl, Me_2NEt, pentane, 0 °C to rt; aldehyde **52**, Et_2O, –78 °C to –25 °C, dr = 85:15, 57%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; aq H_2SO_4, 83%; (c) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C, 95%.

III. Completion of the Synthesis of Aflastatin A[47]

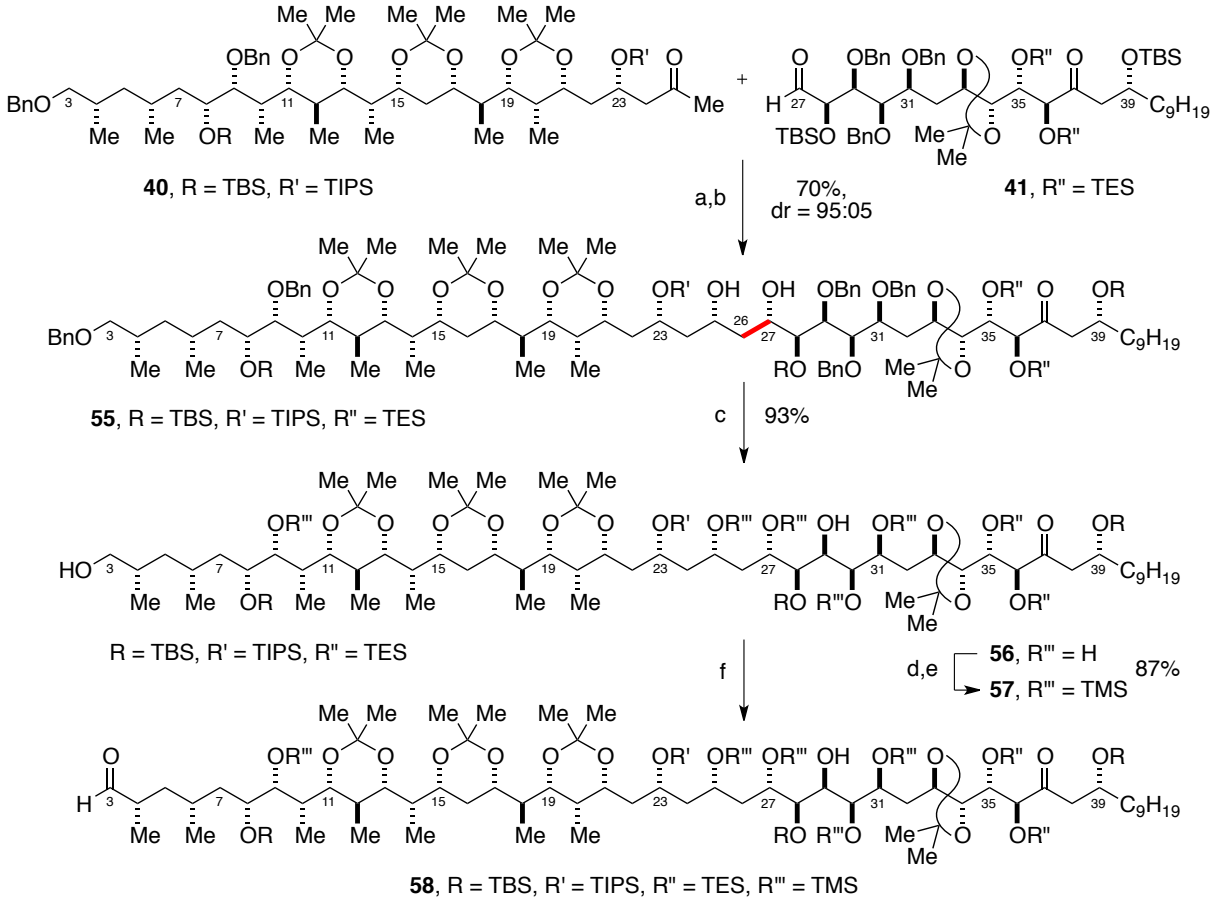
Having completed the syntheses of both the C3–C26 and C27–C48 fragments, we ventured forward with the synthesis of C3–C48 aldehyde **58** (Scheme 4.13). Satisfyingly, chelate-controlled addition of ketone **40** to aldehyde **41** under our soft enolization conditions[33]

(46) (a) Glorius, F. *Development of α-Oxygenated Aldol Methodology and Progress Towards the Synthesis of Aflastatin A*. Postdoctoral Report, Harvard University, **2001**; (b) Evans, D.A.; Glorius, F.; Burch, J.D. *Org. Lett*. **2005**, *7*, 3331–3335.

(47) The synthesis of AsA **1** and its diethylamine salt **1**•Et_2NH was performed by the author.

delivered the desired β-hydroxy ketone with excellent diastereoselection. We immediately reduced the aldol adduct[48] under Prasad's conditions[49,] to afford 1,3-syn diol **55** as a single diastereomer in good overall yield. Both steps were completely chemoselective and eliminated the need to mask the C37 carbonyl.

Scheme 4.13. Synthesis of C3–C48 aldehydes **58**.



Reagents and conditions: (a) $MgBr_2$•OEt_2, PMP, CH_2Cl_2, –5 °C, d.r. = 95:05; (b) Et_2BOMe, $NaBH_4$, THF, MeOH, –78 °C to –55 °C; aq H_2O_2, aq NaOH, MeOH, 0 °C, dr ≥ 95:05, 70% (2 steps); (c) H_2, Pd black, THF, dioxane, H_2O, rt, 93%; (d) TMSCl, py, CH_2Cl_2, 0 °C to rt; (e) PPTS, CH_2Cl_2, iPrOH, 0 °C; Et_3N, 87% (2 steps); (f) SO_3•Py, $EtN(iPr)_2$, DMSO, CH_2Cl_2, –30 °C to –20 °C.

Our synthesis of C3–C48 aldehyde **58** continued with the hydrogenolysis of pentabenzyl ether **55** to produce heptaol **56**. We removed all the benzyl protecting groups in

(48) We observed that the intermediate aldol adduct is subject to retro-aldolization on silica gel. For higher overall yields of diol **55**, we performed the aldol addition and reduction in tandem before purification.

(49) Chen, K.-M.; Hardtmann, G.E.; Prasad, K.; Repič, O; Shapiro, M.J. *Tetrahedron Lett*. **1987**, *28*, 155–158.

advance of installing the tetramic acid because hydrogenation of the C2–C3 alkene of enoyltetramic acids under similar conditions (H_2/Pd) was known.[50] Persilylation of heptaol **56** was then attempted and produced an inseparable yet inconsequential mixture of hexakistrimethylsilyl ethers. We believe persilylation of the C27–C31 pentaol was incomplete, unselective, and potentially complicated by 1,2-silyl migration of the C28 TBS ether.[51,52] Unfortunately, this mixture of differentially silylated material complicated spectral analyses and persisted until global deprotection. Nevertheless, the C3 carbinol was selectively desilylated and oxidized[29,53] to afford a mixture of C3–C48 aldehydes best represented by structure **58**.

With C3–C48 aldehydes **58** in hand, we installed the tetramic acid moiety according to Boeckman's three-step method.[19] Addition of the lithium anion of dioxinone phosphonate **11** to aldehydes **58** in the presence of HMPA[10b,20] provided trisubstituted (*E*) alkenes **59** in moderate yield over two steps (Scheme 4.14). Cycloelimination[19b] of dioxinones **59** in the presence of ammonium salt **9**•HCl led to the formation of β-ketoamides **60** in good yield.

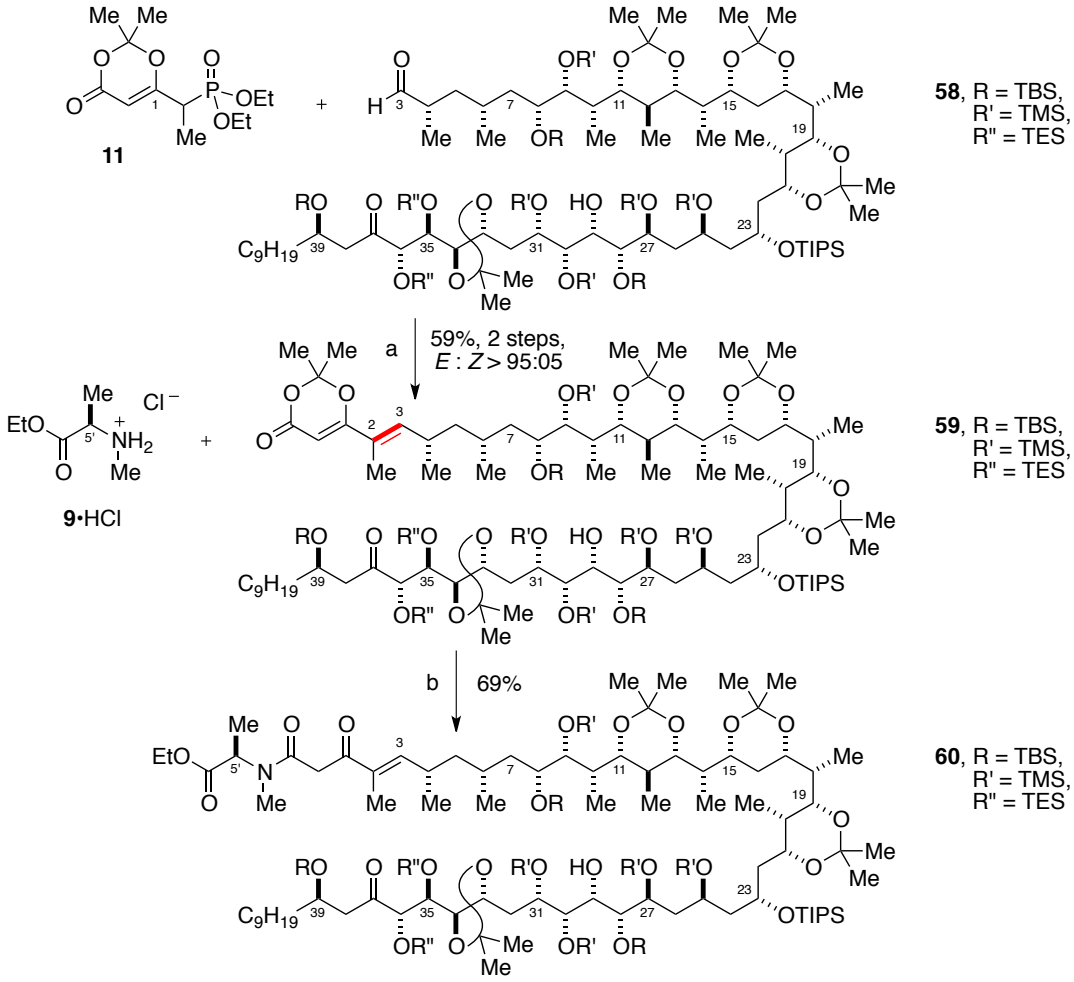
(50) (a) Jones, R.C.F.; Pillainayagam, T.A. *Synlett* **2004**, 2815–2817; (b) Schlenk, A.; Diestel, R.; Sasse, F.; Schobert, R. *Chem. Eur. J.* **2010**, *16*, 2599–2604.

(51) Mulzer, J.; Schöllhorn, B. *Angew. Chem., Int. Ed.* **1990**, *29*, 431–432.

(52) We believe regioisomers are formed in this step due to the inconsequential 1,2-migration of the *tert*-butyldimethylsilyl (TBS) group(s) at C28 and/or (less likely) C8.

(53) Selective oxidation of the C3 carbinol may also be achieved with TEMPO as catalytic oxidant, but we observed that aldehydes **58** were more prone to decomposition during workup. See: De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041–3043.

Scheme 4.14. Synthesis of β-ketoamides **60**.



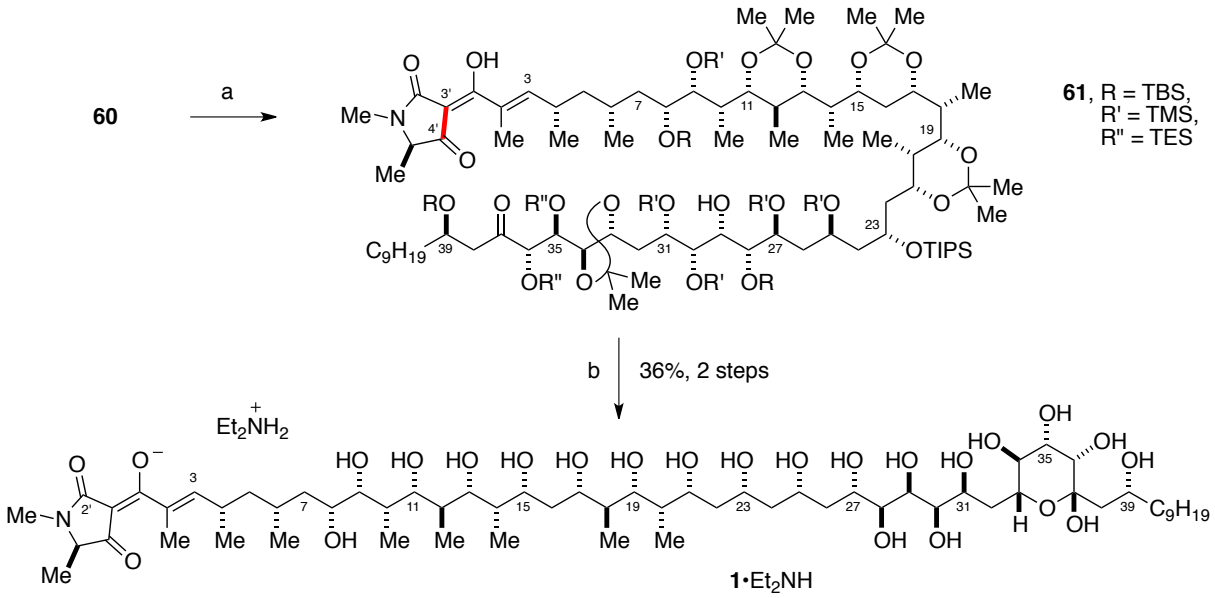
Reagents and conditions: (a) phosphonate **11**, LDA, THF, –78 °C to 0 °C; HMPA, –78 °C; aldehydes **58**, –78 °C to rt, *E*:*Z* > 95:05, 59% (2 steps); (b) 4 Å MS, PhMe, 110 °C, 69%.

Modified Lacey-Dieckmann cyclization[14] of β-ketoamides **60** was then induced by potassium trimethylsilanolate and produced tetramic acids **61** without appreciable elimination of the C39 silyl ether (Scheme 4.15). Removal of the acetonide and silyl protecting groups[25] converged the isomer mixture of tetramic acids and completed the synthesis of AsA (**1**). The free tetramic acid was converted to its corresponding diethylammonium salt **1**•Et_2NH upon purification.

Spectroscopic data for diethylammonium tetramate **1**•Et_2NH was identical in all respects (^{1}H-NMR, ^{13}C-NMR, IR, HRMS) to those reported by the isolation group for the

naturally derived AsA salt.[26] The optical rotation of the synthetic material ($[\alpha]_D^{26}$ –2.8° (*c* = 0.55, DMSO)) was also in agreement with that reported for the naturally derived sample ($[\alpha]_D^{19}$ –2.6° (*c* = 0.545, DMSO)).

Scheme 4.15. Synthesis of the diethylamine salt of AsA (**1**•Et_2NH).



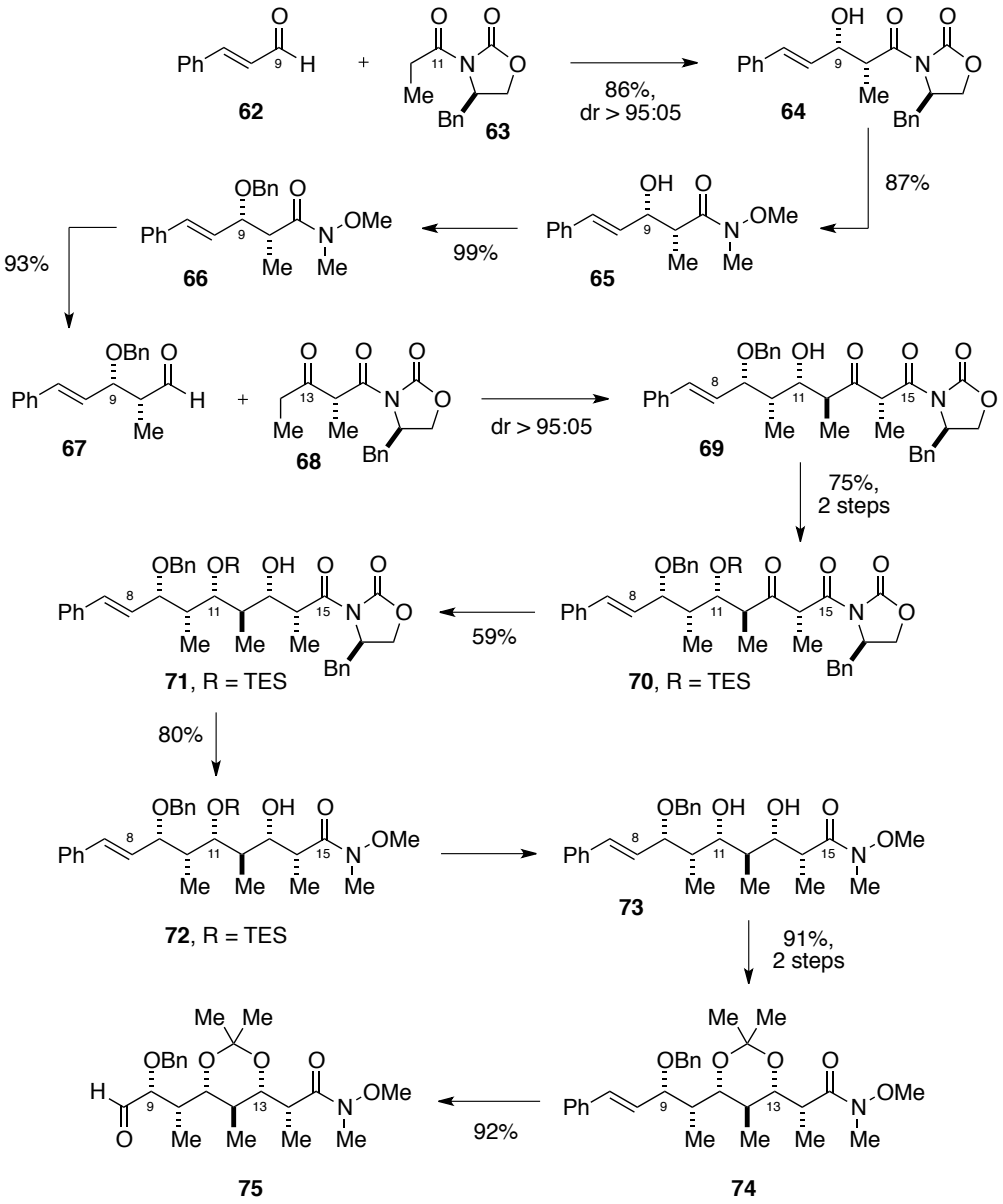
Reagents and conditions: (a) KOTMS, TMSOH, THF, 0 °C; (b) aq H_2SiF_6, MeCN, CH_2Cl_2, 0 °C to rt; Et_2NH, MeOH, H_2O, rt (purification), 36% (2 steps).

Herein we have described the asymmetric synthesis of aflastatin A (**1**) in 32 linear steps and 0.69% overall yield from methacrolein, and in 91 total steps from commercially available starting materials. Our synthesis features several complex diastereoselective fragment couplings, including an anti-Felkin-selective α-oxygenated aldol reaction, two trityl-catalyzed Felkin-selective aldol additions, and two chelate-controlled/soft enolization-based aldol couplings. We hope our work involving oxygenated enolates, trityl catalysis, and soft enolization with magnesium clearly demonstrates the reliability of these methods in complex settings, as well as their potential applicability to the large-scale production of chiral building blocks for stereoselective organic synthesis.

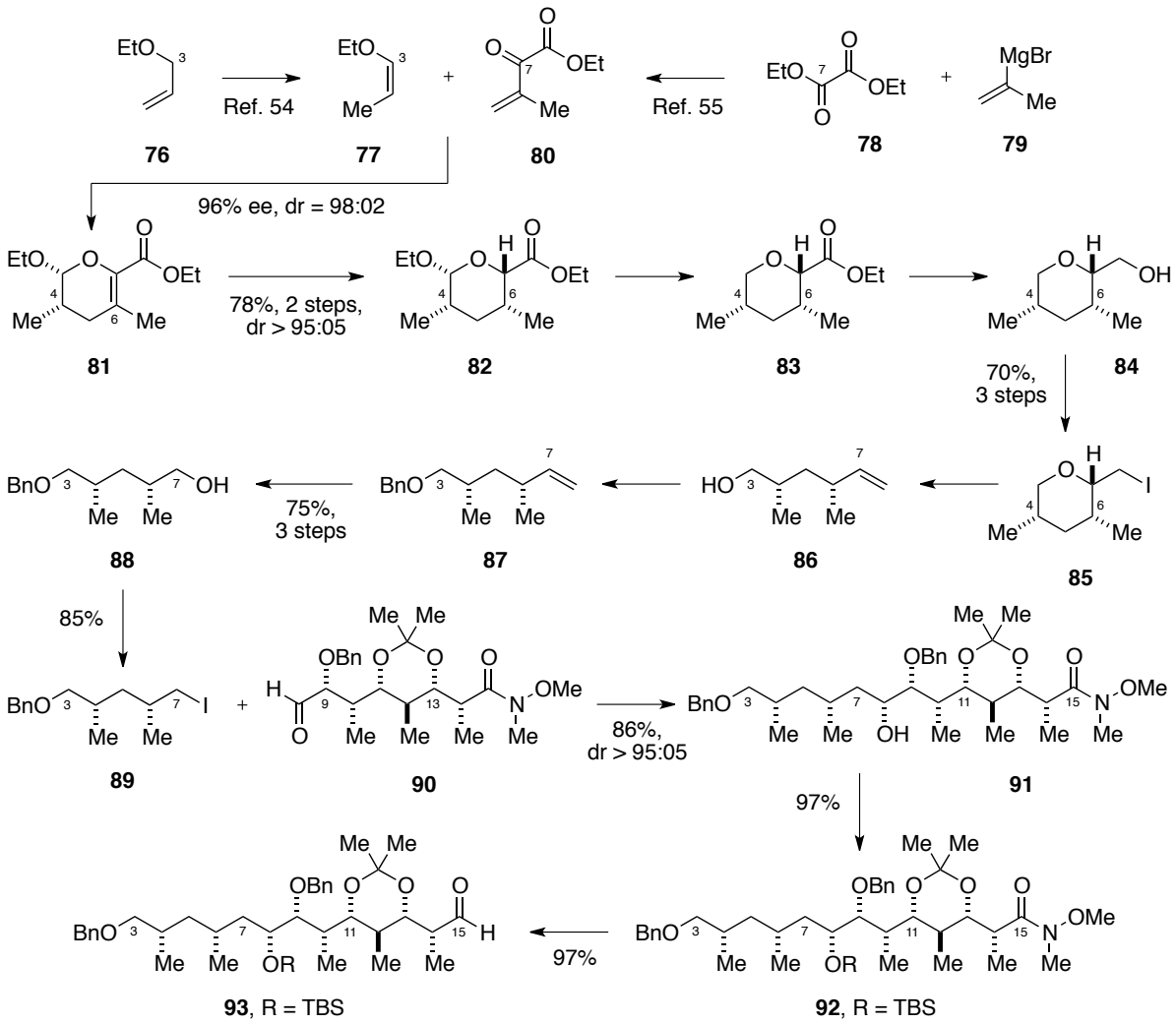
IV. Graphical Summary of the Total Synthesis of Aflastatin A

Synthesis of the C3–C26 Ketone

Synthesis of C8–C15 Aldehyde 75



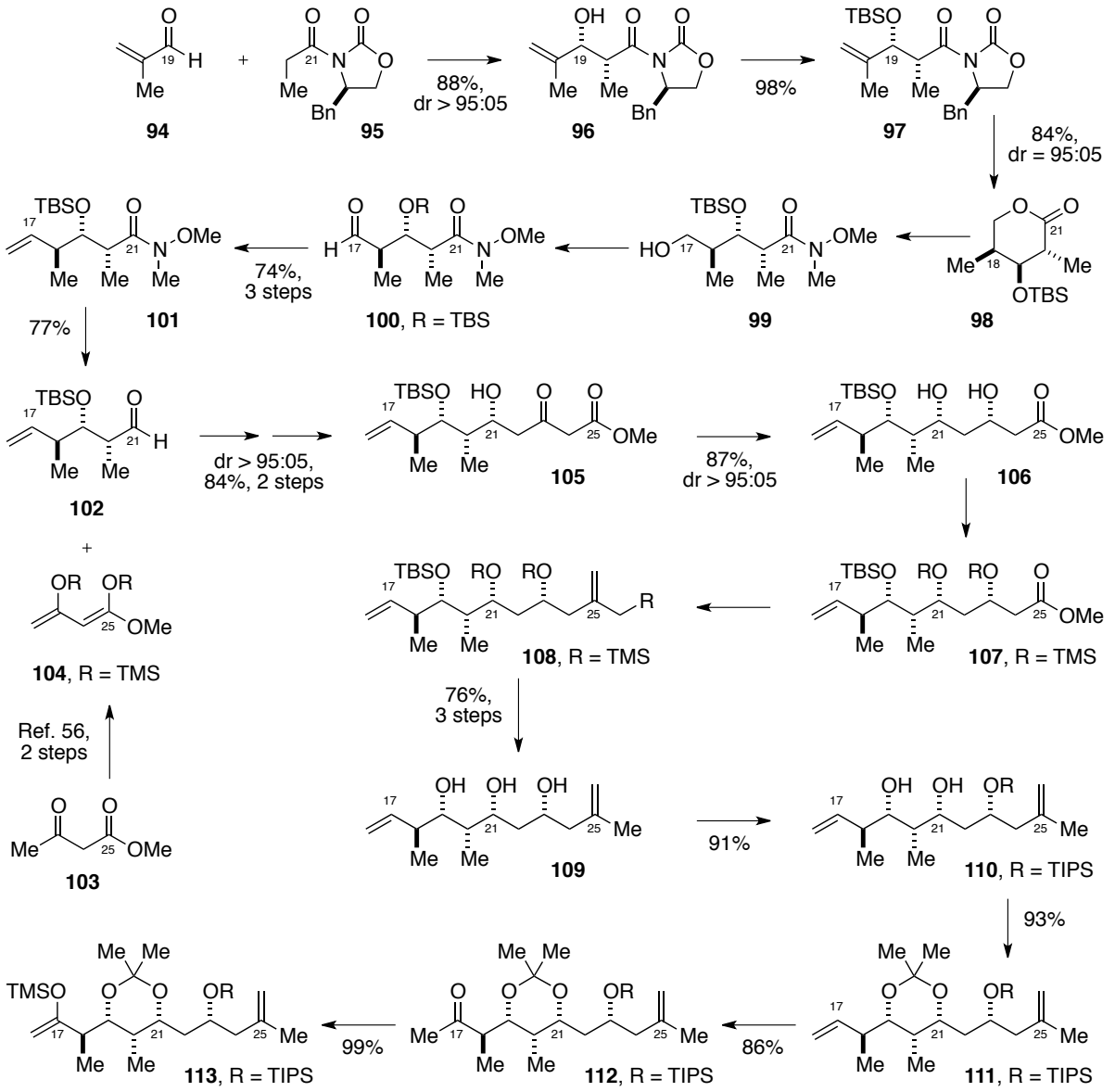
Synthesis of C3–C15 Aldehyde 93[54,55]



(54) Dunn, T.B. *Synthesis of the C21–C40 Fragment of Azaspiracid-1*. Ph.D. Thesis, Harvard University, **2005** and references cited therein.

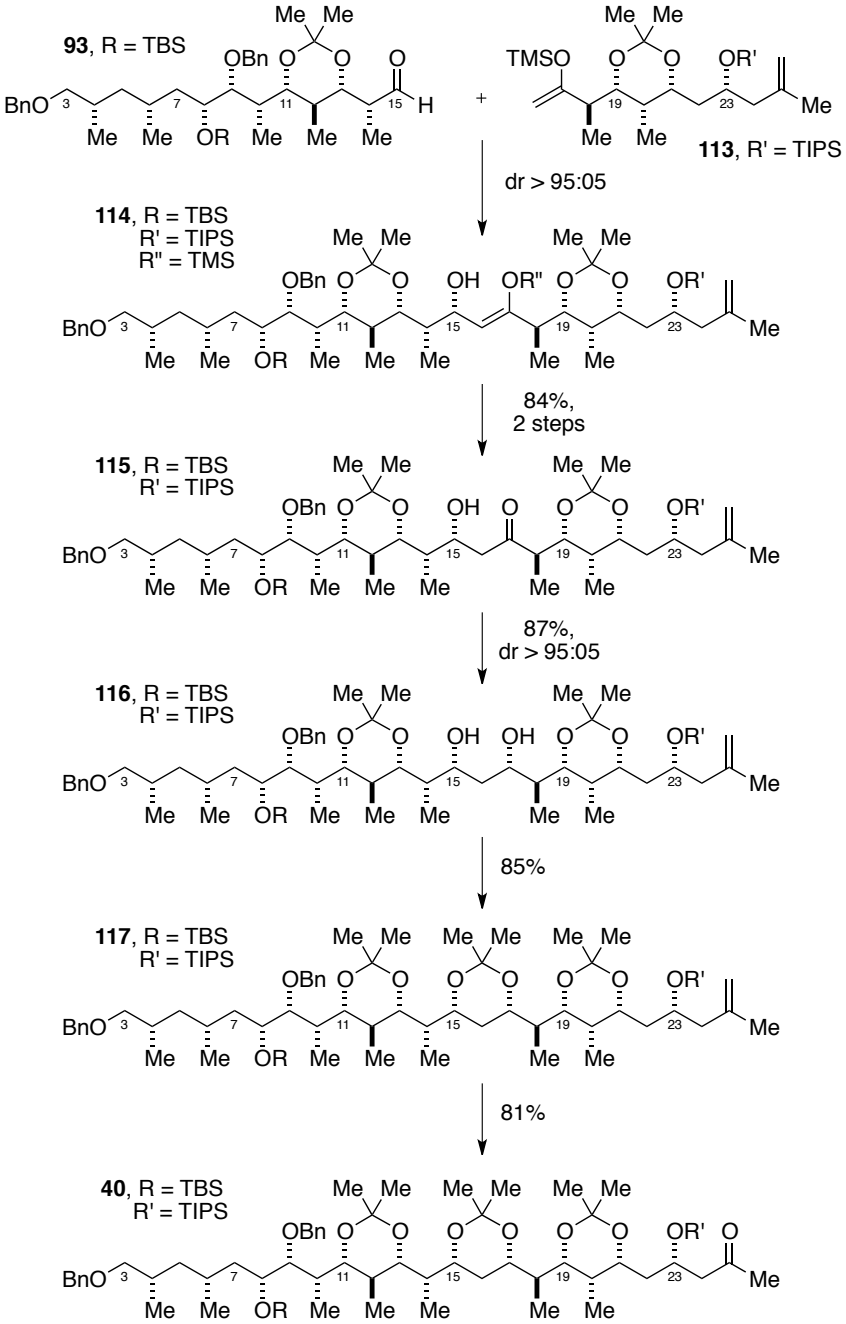
(55) (a) Ref. 54; (b) Rambaud, M.; Bakasse, M.; Duguay, G.; Villieras, J. *Synthesis* **1988**, 564–566.

Synthesis of C16–C26 Enolsilane 113[56]



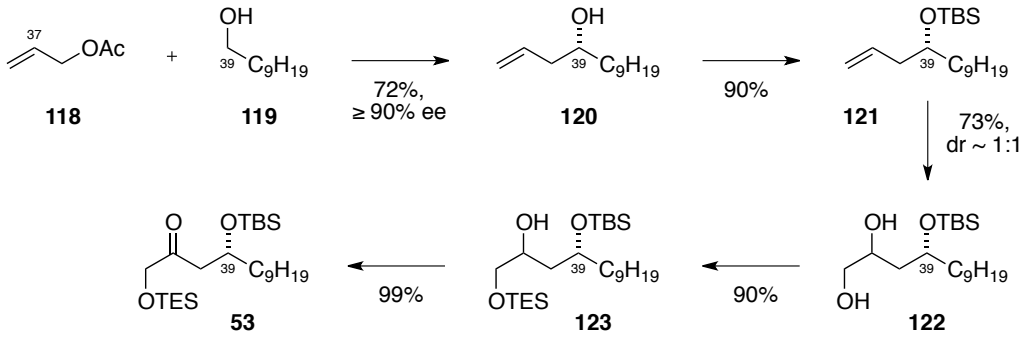
(56) (a) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578–579; (b) Brownbridge, P.; Chan, T.-H.; Brook, M.A.; Kang, G.J. *Can. J. Chem.* **1983**, *61*, 688–693.

Synthesis of C3–C26 Ketone 40

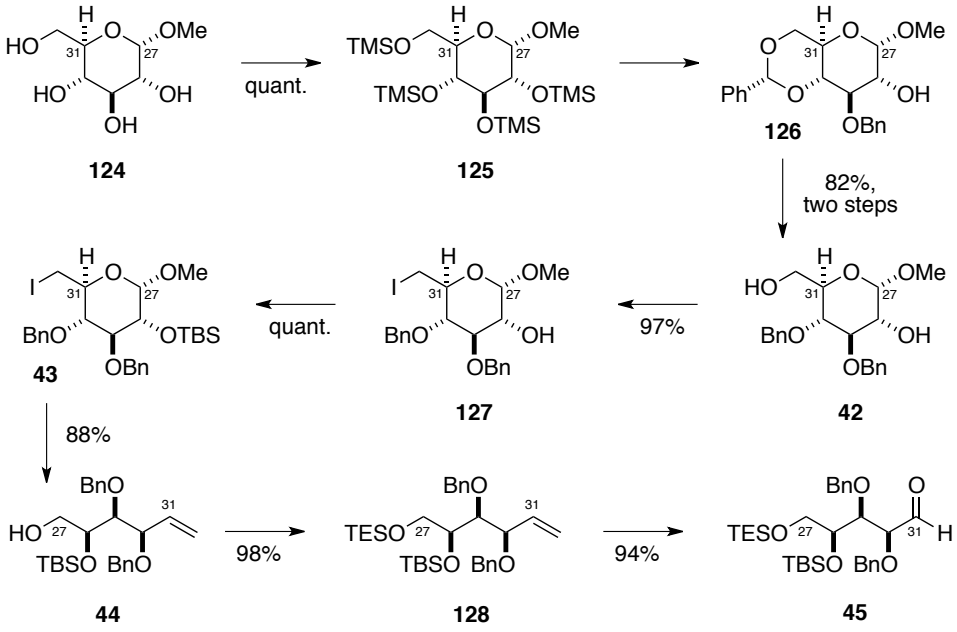


Synthesis of the C27–C48 Aldehyde

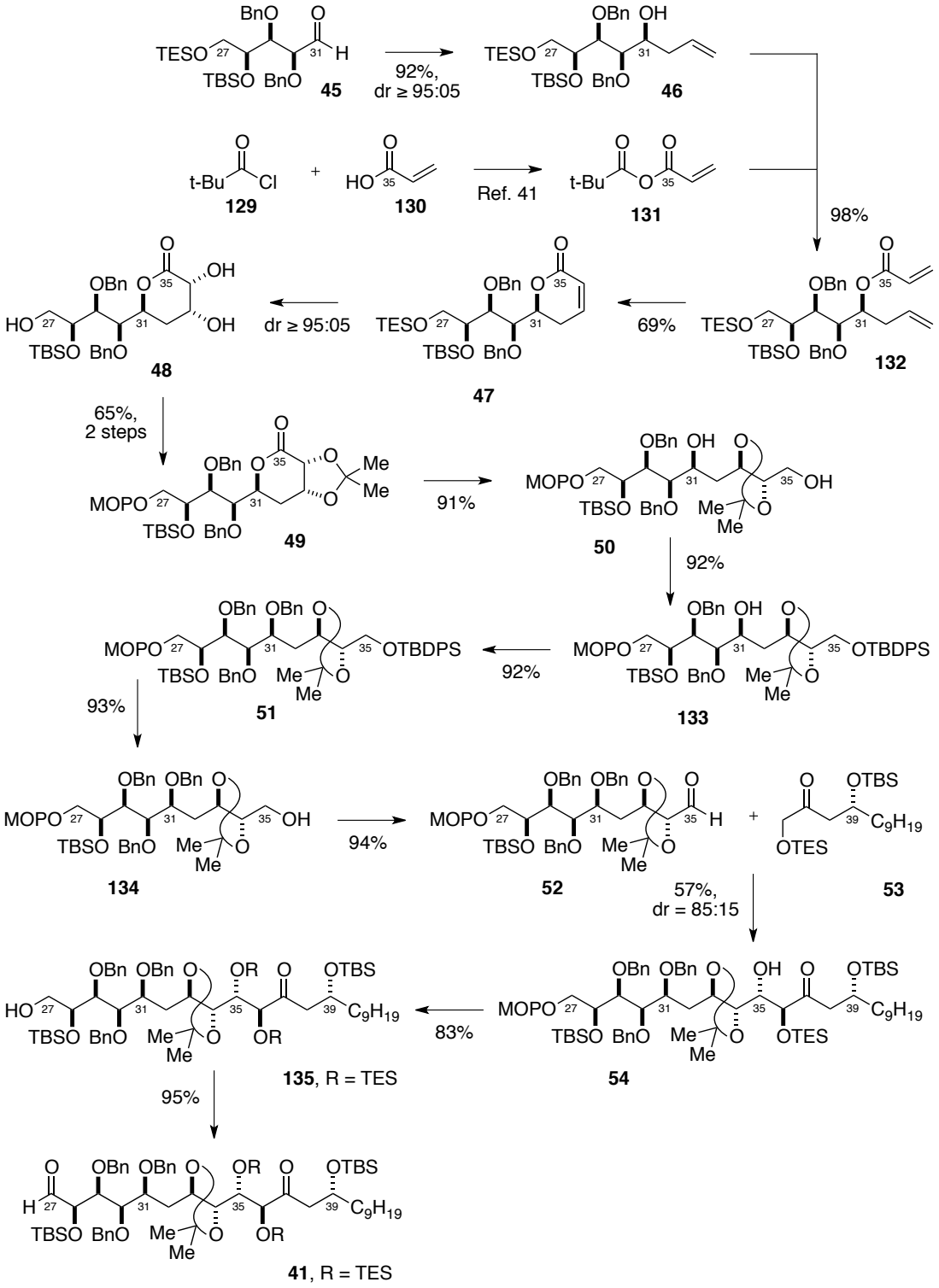
Synthesis of C36–C48 Ketone 53



Synthesis of C27–C31 Aldehyde 45

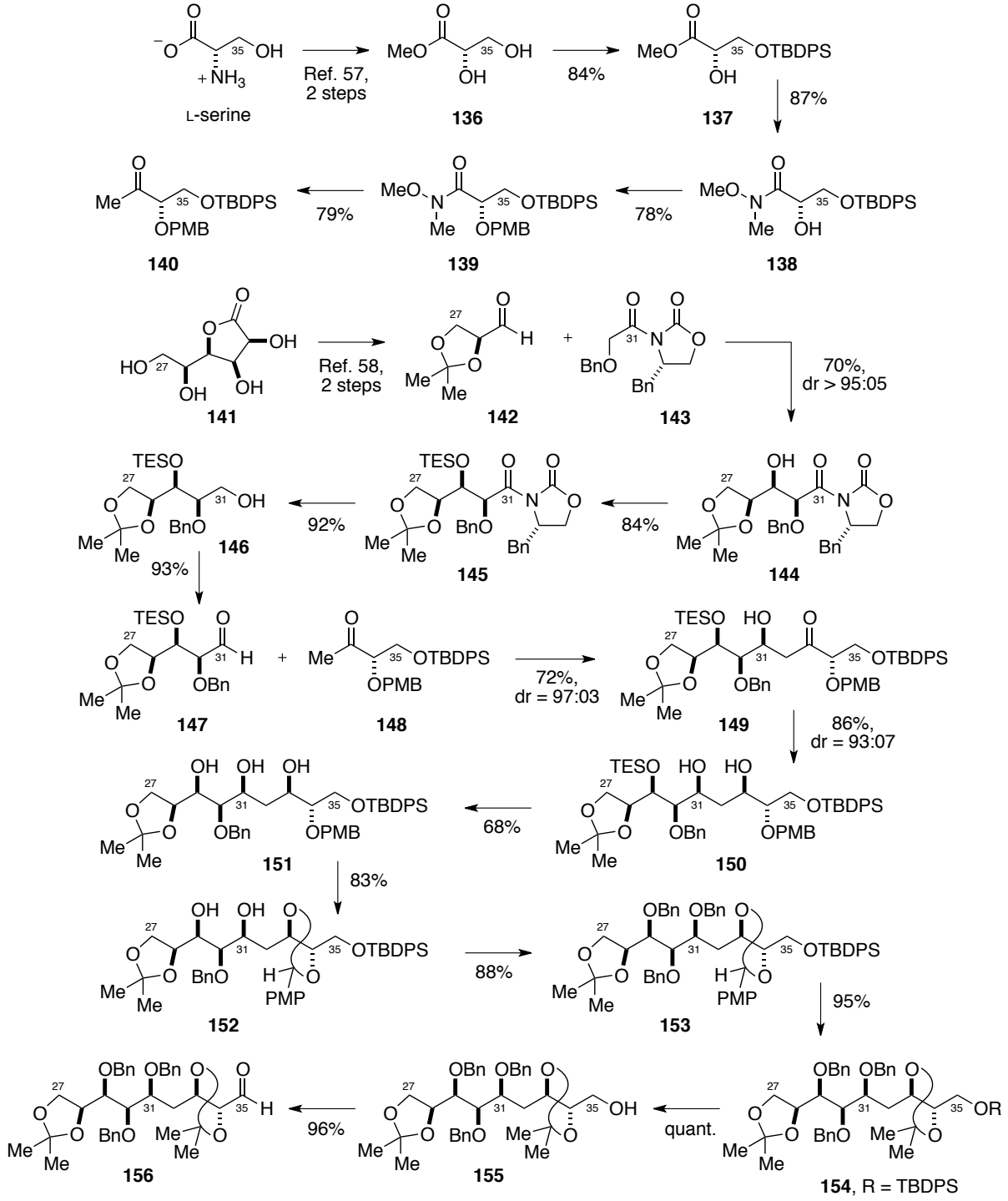


Synthesis of C27–C48 Aldehyde 41



Alternative Synthesis of the C27–C48 Aldehyde

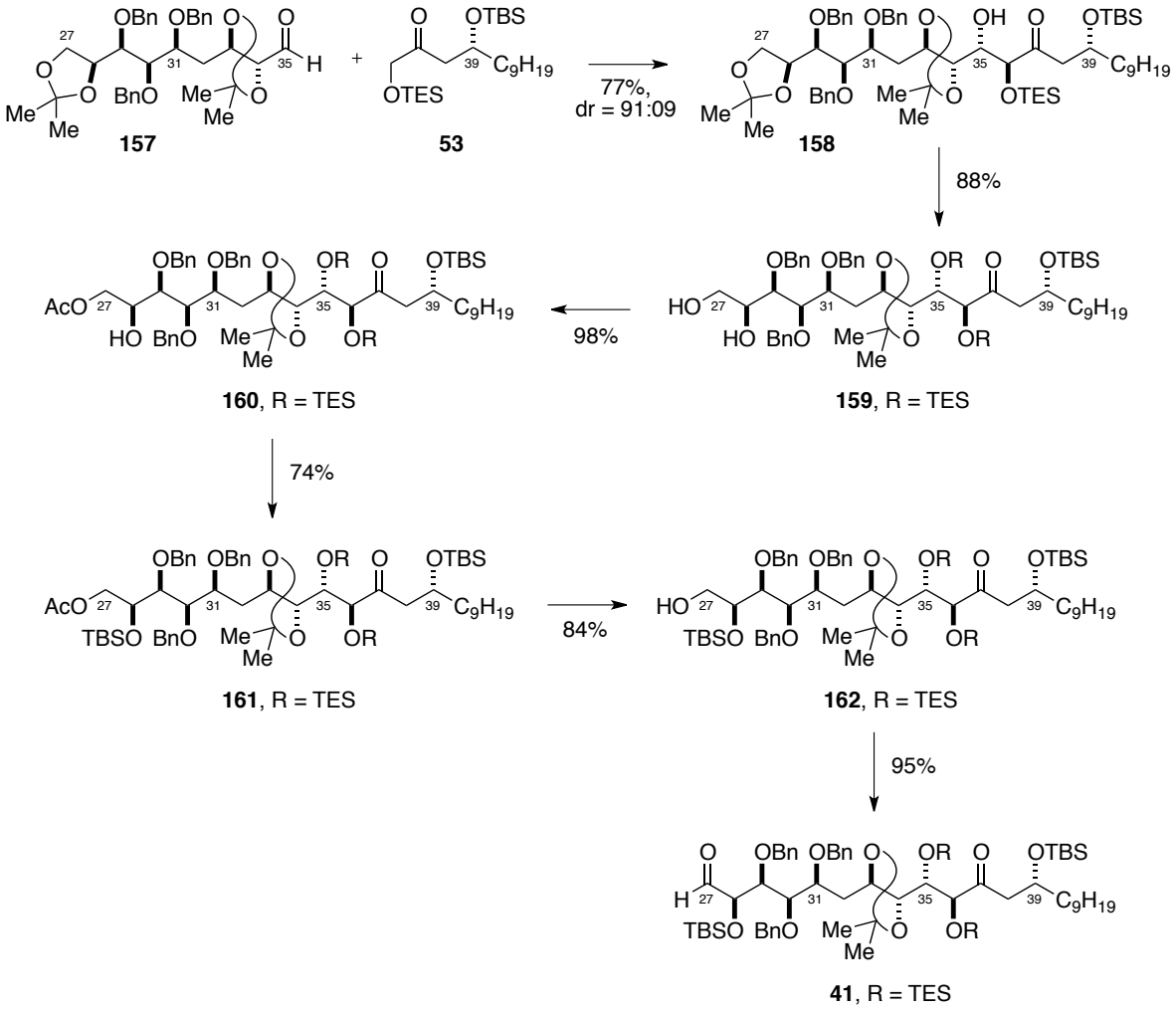
Synthesis of C27–C35 Aldehyde 156[57,58]



(57) Hirth, G.; Walther, W. *Helv. Chim. Acta* **1985**, *68*, 1863–1871.

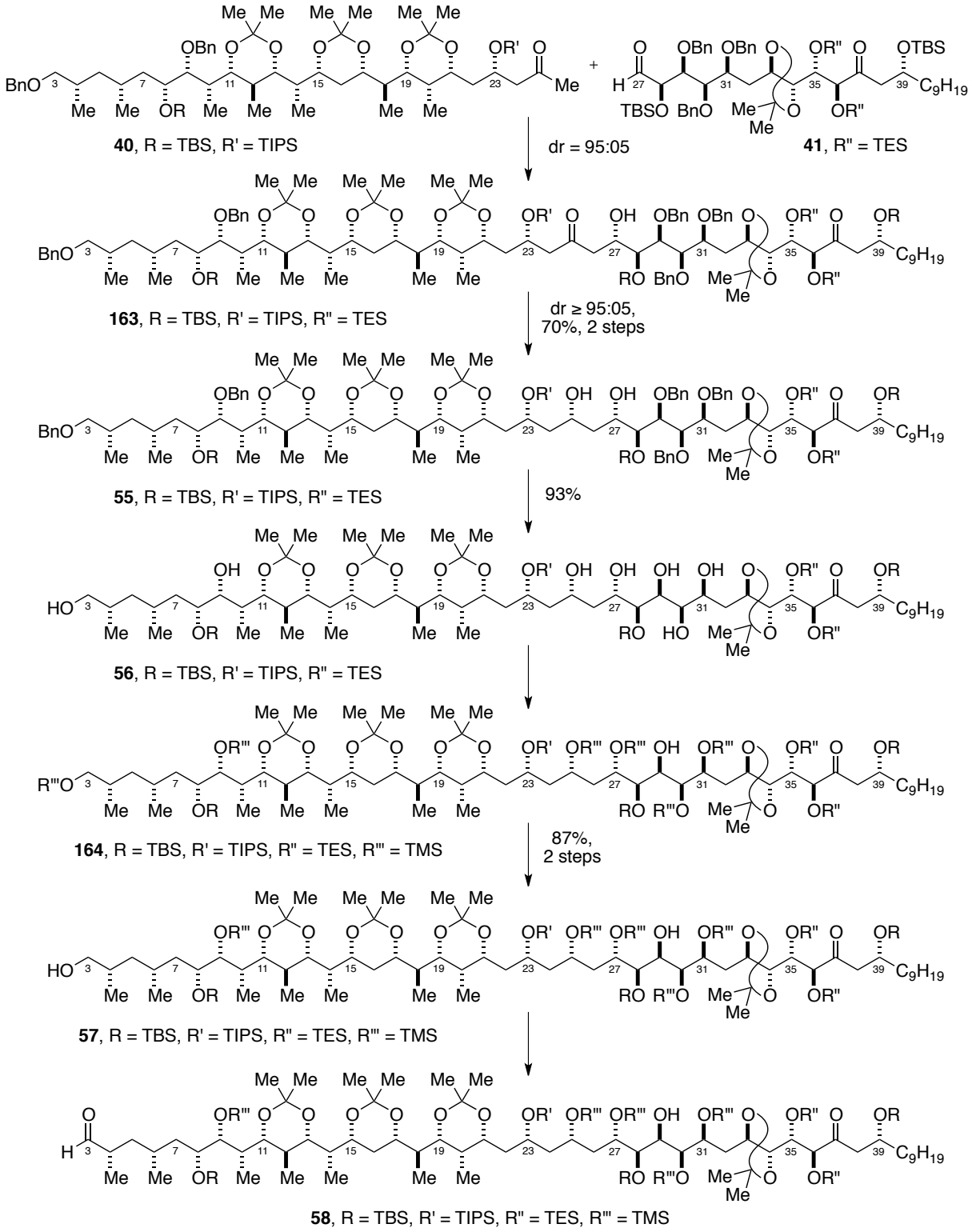
(58) Hubschwerlen, C.; Specklin, J.-L.; Higelin, J. *Org. Synth.* **1995**, *72*, 1–5.

Synthesis of C27–C48 Aldehyde 41

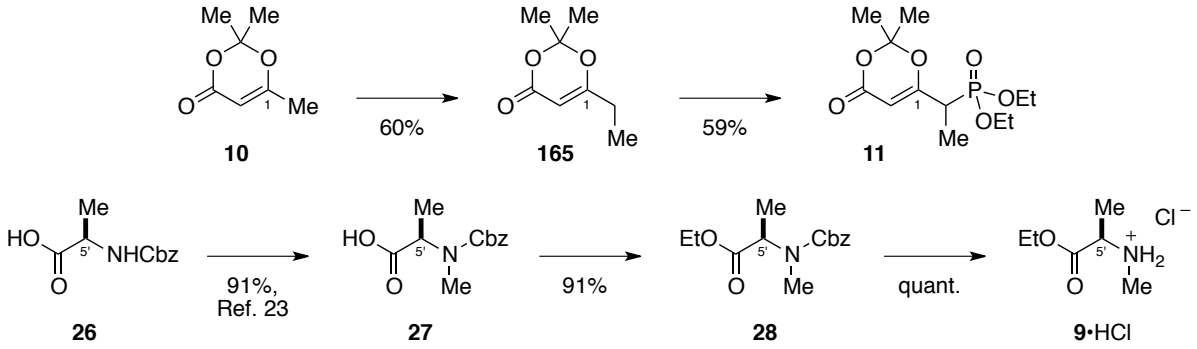


Synthesis of Aflastatin A

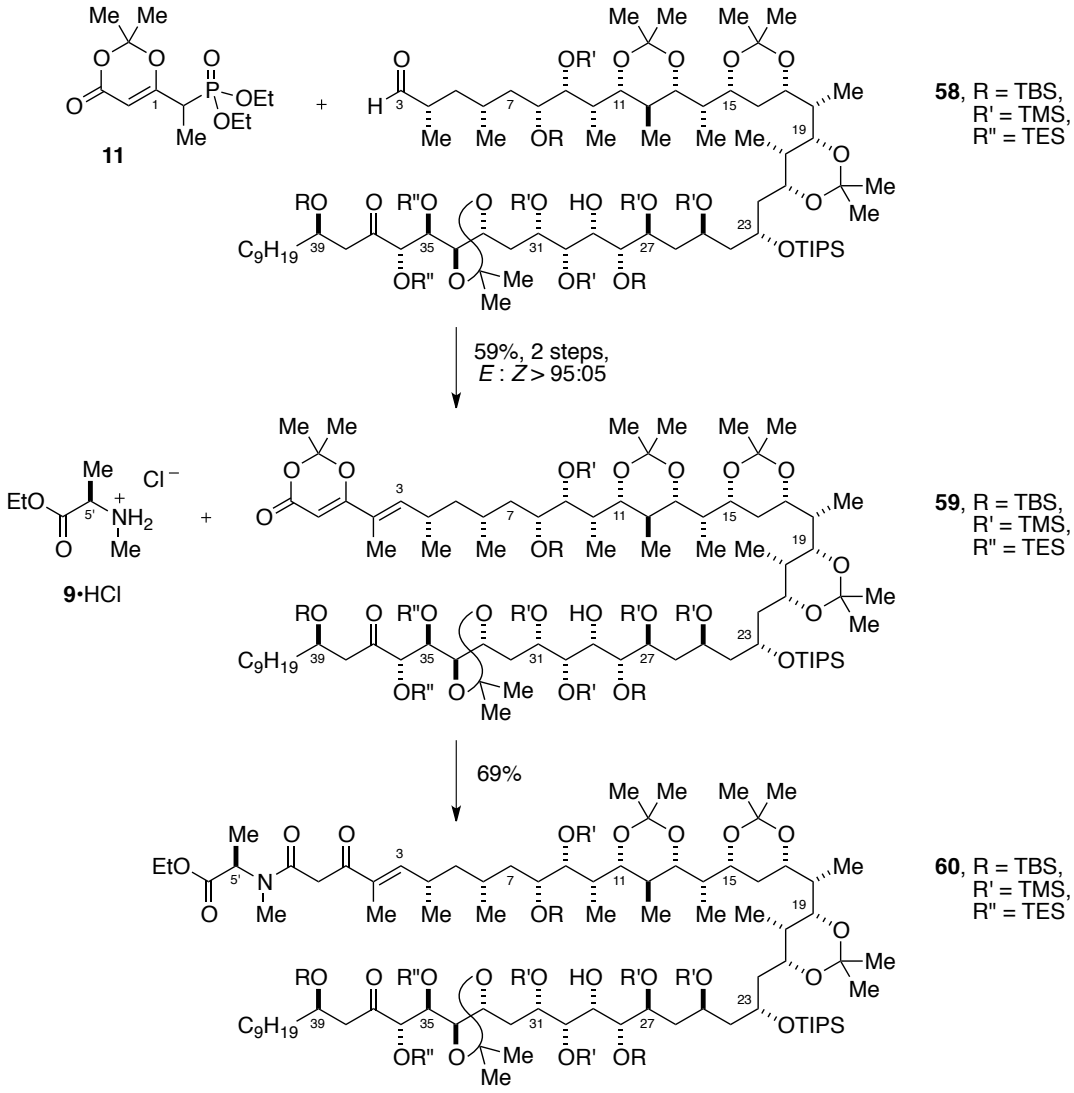
Synthesis of C3–C48 Aldehydes 58



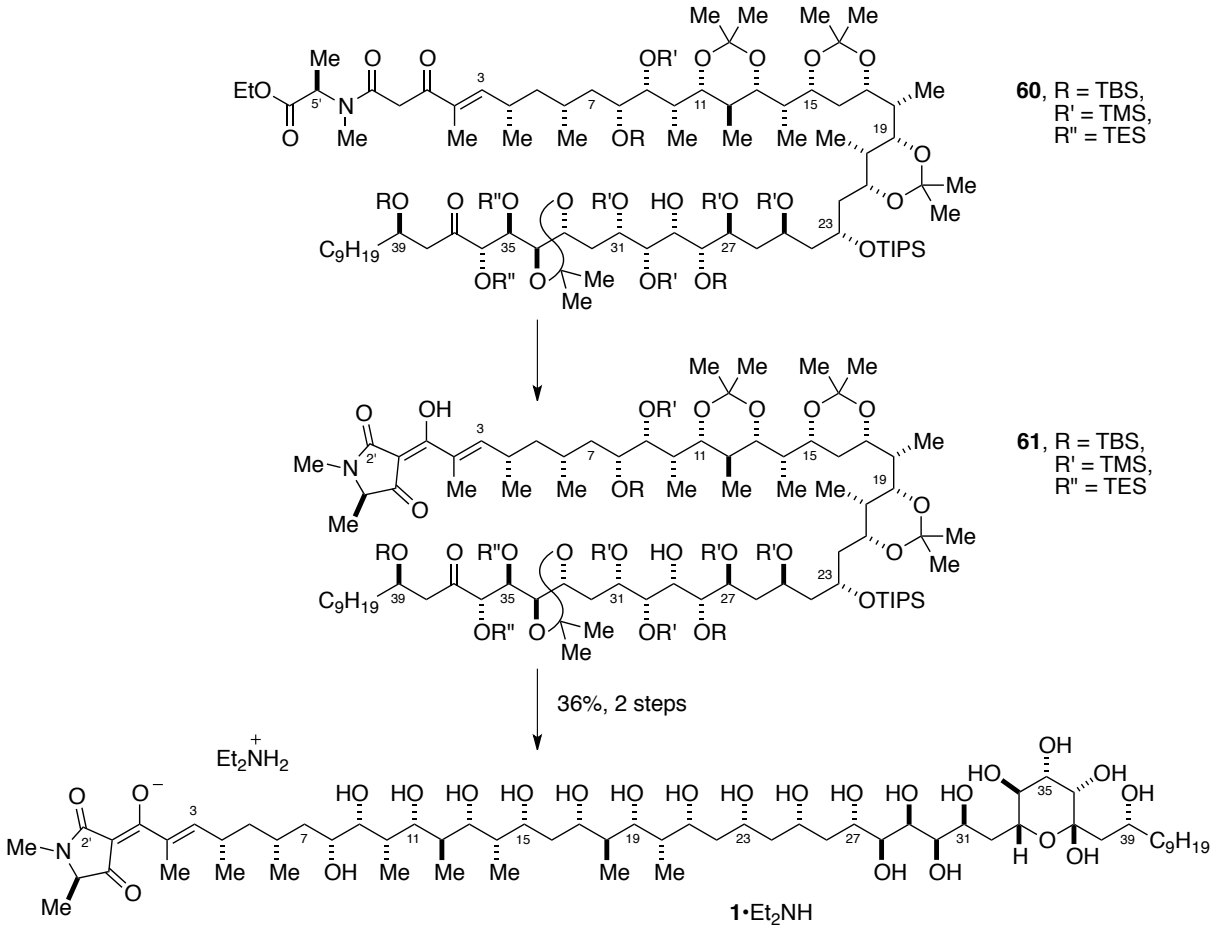
Syntheses of Dioxinone Phosphonate 11 and Ammonium Salt 9•HCl



Synthesis of β-Ketoamides 60

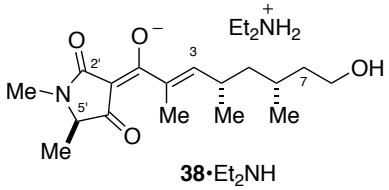


Synthesis of Aflastatin A (1) and its Diethylamine Salt (1•Et_2NH)



IV. Experimental Section

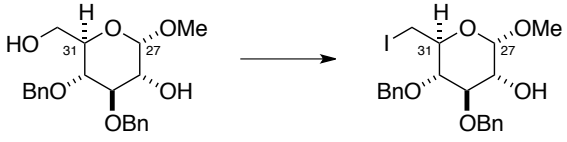
Spectroscopic Data for Tetramic Acid Degradation Fragment 38•Et_2NH



38•Et_2NH

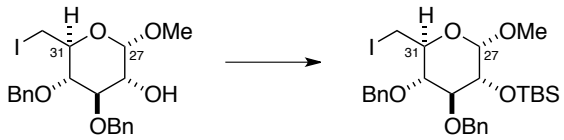
Diethylammonium (1*Z*,2*E*,4*S*,6*R*)-1-((*R*)-1,5-dimethyl-2,4-dioxopyrrolidin-3-ylidene)-8-hydroxy-2,4,6-trimethyloct-2-en-1-olate (38•Et_2NH). White solid; ^{1}H-NMR (600 MHz, CD_3OD) δ 5.69 (d, *J* = 9.8 Hz, 1H, C_3-**H**), 3.59 (ddd, *J* = 10.8, 6.6, 6.6 Hz, 1H, one of C_8-$\mathbf{H_2}$), 3.54 (ddd, *J* = 11.0, 6.7, 6.6 Hz, 1H, one of C_8-$\mathbf{H_2}$), 3.46 (q, *J* = 6.7 Hz, 1H, $C_{5'}$-**H**), 3.02 (q, *J* = 7.3 Hz, 4H, $NC\mathbf{H_2}CH_3$), 2.85 (s, 3H, $C_{7'}$-$\mathbf{H_3}$), 2.66–2.63 (m, 1H, C_4-**H**), 1.83 (d, *J* = 1.2 Hz, 3H, C_9-$\mathbf{H_3}$), 1.71–1.68 (m, 1H, C_6-**H**), 1.50–1.46 (m, *J* = 6.7, 6.6 Hz, 1H, one of C_7-$\mathbf{H_2}$), 1.38–1.31 (m, *J* = 7.0, 6.7 Hz, 2H, one of C_5-$\mathbf{H_2}$, and one of C_7-$\mathbf{H_2}$), 1.27 (t, *J* = 7.3 Hz, 6H, $NCH_2C\mathbf{H_3}$), 1.26 (d, *J* = 7.3 Hz, 3H, $C_{6'}$-$\mathbf{H_3}$), 1.12 (ddd, *J* = 13.3, 9.1, 4.4 Hz, 1H, one of C_5-$\mathbf{H_2}$), 0.99 (d, *J* = 6.6 Hz, 3H, C_{10}-$\mathbf{H_3}$), 0.90 (d, *J* = 6.6 Hz, 3H, C_{11}-$\mathbf{H_3}$); ^{13}C-NMR (125 MHz, CD_3OD) δ 196.0 (C4'), 195.7 (C1), 175.8 (C2'), 143.2 (C3), 137.0 (C2), 101.0 (C3'), 61.8 (C5'), 60.9 (C8), 46.2 (C5), 43.4 ($N\underline{C}H_2CH_3$), 41.8 (C7), 31.7 (C4), 28.3 (C6), 26.9 (C7'), 21.1 (C10), 20.4 (C11), 16.3 (C6'), 13.6 (C9), 11.6 ($NCH_2\underline{C}H_3$); HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{28}NO_4$ $[M+H]^+$: 310.2013, found: 310.2015.

Synthesis of the C27–C35 Aldehyde



(2*S*,3*R*,4*R*,5*S*,6*S*)-4,5-Bis(benzyloxy)-6-(iodomethyl)-2-methoxytetrahydro-2*H*-pyran-3-ol (127). To a solution of diol **42** (9.8 g, 26 mmol, 1.0 equiv), imidazole (5.4 g, 79 mmol, 3.0 equiv), and triphenylphosphine (10.7 g, 40.7 mmol, 1.55 equiv) in 2:1 PhMe/MeCN (131 mL, 0.2 M wrt **42**) at rt was added iodine (10 g, 39 mmol, 1.5 equiv) in three portions. The reaction mixture was stirred at rt for 3 h, quenched with brine (100 mL), and then diluted with H_2O (10 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer extracted

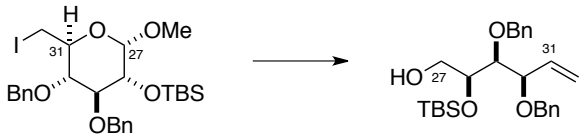
with Et_2O (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 5:1 → 4:1 → 3:1 hexanes/EtOAc) afforded iodide **127** (12.3 g, 97% yield) as a white solid. $[\alpha]_D^{25}$ +95.4° (*c* = 2.3, CH_2Cl_2); IR (neat) 3424 (br), 3029, 2924, 1497, 1453, 1399, 1361, 1325, 1214, 1192, 1140, 1087, 1046, 733, 696 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.39–7.30 (m, 10H, Ar**H**), 4.95 (d, *J* = 11.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.94 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.84 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.78 (d, *J* = 3.8 Hz, 1H, C_{27}-**H**), 4.72 (d, *J* = 11.0 Hz, 1H, one of –OC**H**$_2$Ph), 3.80 (dd, *J* = 9.2, 8.9 Hz, 1H, C_{29}-**H**), 3.71 (ddd, *J* = 8.8, 8.6, 3.8 Hz, 1H, C_{28}-**H**), 3.51 (dd, *J* = 10.5, 2.6 Hz, 1H, one of C_{32}-**H**), 3.48 (ddd, *J* = 9.1, 6.4, 2.6 Hz, 1H, C_{31}-**H**), 3.48 (s, 3H, –OC**H**$_3$), 3.36 (dd, *J* = 9.2, 8.9 Hz, 1H, C_{30}-**H**), 3.32 (dd, *J* = 10.5, 6.3 Hz, 1H, one of C_{32}-**H**), 2.16 (d, *J* = 8.6 Hz, 1H, C_{28}-O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.4, 137.9, 128.5, 128.5, 127.9, 127.9, 127.8, 99.3, 82.8, 81.2, 75.4, 75.3, 73.1, 69.7, 55.5, 7.3; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{25}INaO_5$ $[M+Na]^+$: 507.06389, found: 507.06416.



127 **43**

(((2*S*,3*R*,4*S*,5*S*,6*S*)-4,5-Bis(benzyloxy)-6-(iodomethyl)-2-methoxytetrahydro-2*H*-pyran-3-yl)oxy)(*tert*-butyl)dimethylsilane (43). To a solution of carbinol **127** (12.3 g, 25.3 mmol, 1.0 equiv) and imidazole (3.5 g, 51 mmol, 2.0 equiv) in CH_2Cl_2 (25 mL, 1.0 M wrt **127**) at 0 °C was added *tert*-butylchlorodimethylsilane (5.7 g, 38 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 2 h, slowly warmed to rt over 2 h, stirred at rt for 8 h, quenched at 0 °C with brine (40 mL), and diluted with Et_2O (150 mL) and H_2O (20 mL). The layers were separated and the organic layer washed with 1:1 H_2O/brine (2 x 50 mL), dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 3% → 4% → 5% EtOAc in hexanes) afforded silyl ether **43** (15.2 g, quant. yield) as a clear, colorless oil. $[\alpha]_D^{23}$ +56.1° (*c* = 2.9, CH_2Cl_2); IR (neat) 3064, 3032, 2929, 2857, 1455, 1360, 1254, 1196, 1151, 1090, 1051, 1000, 862, 838, 778, 735, 698 cm^{-1}; ^{1}H-NMR (600 MHz, C_6D_6) δ 7.32 (m, 2H, Ar**H**), 7.20–7.05 (m, 8H, Ar**H**), 4.95 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.85 (d, *J* = 11.3 Hz, 1H, one of –OC**H**$_2$Ph), 4.74 (d, *J* = 11.6 Hz, 1H, one of –

OC**H**$_2$Ph), 4.57 (m, 1H, C_{27}-**H**), 4.56 (d, *J* = 11.3 Hz, 1H, one of –OC**H**$_2$Ph), 4.03 (ddd, *J* = 9.1, 9.1, 2.2 Hz, 1H, C_{29}-**H**), 3.77 (ddd, *J* = 9.4, 3.6, 1.8 Hz, 1H, C_{28}-**H**), 3.47 (ddd, *J* = 6.6, 2.3, 1.6 Hz, 1H, C_{31}-**H**), 3.33 (dd, *J* = 9.2, 1.6 Hz, 1H, C_{30}-**H**), 3.30 (dd, *J* = 10.5, 2.5 Hz, 1H, one of C_{32}-**H**), 3.20 (s, 3H, –OC**H**$_3$), 3.12 (dd, *J* = 10.6, 6.5 Hz, 1H, one of C_{32}-**H**), 0.93 (s, 9H, C(C**H**$_3$)$_3$), 0.03 (s, 3H, one of SiC**H**$_3$), –0.02 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, C_6D_6) δ 139.4, 138.8, 128.5, 128.5, 128.4, 127.9, 127.8, 127.5, 127.5, 100.5, 82.5, 82.1, 75.5, 75.2, 74.6, 70.0, 55.3, 25.9, 18.2, 8.0, –4.5, –4.6; HRMS (ESI-TOF) *m/z* calcd for $C_{27}H_{39}INaO_5Si$ $[M+Na]^+$: 621.15036, found: 621.14896.

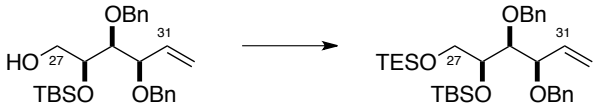


43 **44**

(2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)hex-5-en-1-ol (44). To a solution of iodide **43** (3.7 g, 6.2 mmol, 1.0 equiv) in 9:1 THF/H_2O (77 mL, 0.08 M wrt **43**) at rt was added preactivated zinc dust[59] (4.0 g, 62 mmol, 10 equiv). The reaction mixture was sonicated at 40–45 °C for 3 h, then cooled to 0 °C and charged with sodium borohydride (0.77 g, 20 mmol, 3.3 equiv) in six portions over 1 h. The resulting suspension was stirred at 0 °C for an additional 15 min, slowly quenched with 1 M $NaHSO_4$ (40 mL), diluted with Et_2O (40 mL), warmed to rt, and filtered through Celite®. The filter cake was rinsed with Et_2O (3 x 50 mL) and sat. aq NH_4Cl (3 x 50 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 150 mL). The combined organic extracts were dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 6% → 7% → 8% → 9% EtOAc in hexanes) afforded carbinol **44** (2.4 g, 88% yield) as a clear, colorless oil. $[\alpha]_D^{23}$ –12.1° (*c* = 1.1, CH_2Cl_2); IR (neat) 3466 (br), 3072, 3032, 2931, 2861, 1461, 1396, 1361, 1253, 1209, 1055, 928, 834, 776, 735, 697 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.36–7.28 (m, 10H, two of Ar**H**), 5.94 (ddd, *J* = 17.4, 10.4, 7.3 Hz, 1H, C_{31}-**H**), 5.31 (dd, *J* = 17.4, 0.8 Hz, 1H, one of C_{32}-**H**), 5.29 (dd, *J* = 10.5, 0.8 Hz, 1H, one of C_{32}-**H**), 4.71 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.68 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.64 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.38 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.09 (ddd, *J* =

(59) Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444–8452.

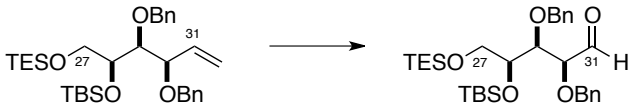
7.3, 3.8, 0.7 Hz, 1H, C_{30}-**H**), 3.76 (ddd, *J* = 5.7, 4.8, 4.5 Hz, 1H, C_{28}-**H**), 3.67 (ddd, *J* = 11.7, 5.7, 5.2 Hz, 1H, one of C_{27}-**H**), 3.59 (ddd, *J* = 11.7, 7.5, 4.2 Hz, 1H, one of C_{27}-**H**), 3.52 (dd, *J* = 5.9, 3.9 Hz, 1H, C_{29}-**H**), 2.37 (dd, *J* = 7.3, 5.8 Hz, 1H, C_{27}-O**H**), 0.88 (s, 9H, C(C**H**$_3$)$_3$), 0.05 (s, 3H, one of SiC**H**$_3$), 0.01 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.3, 137.9, 135.7, 128.3, 128.3, 128.1, 128.1, 127.6, 118.1, 82.6, 79.3, 74.3, 72.6, 70.6, 64.0, 25.8, 18.0, –4.7, –4.7; HRMS (ESI-TOF) *m/z* calcd for $C_{26}H_{38}NaO_4Si$ [M+Na]$^+$: 465.24316, found: 465.24360.



44 **128**

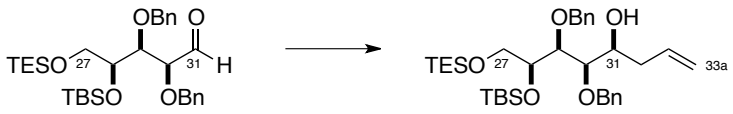
(*S*)-5-((1*S*,2*R*)-1,2-Bis(benzyloxy)but-3-en-1-yl)-8,8-diethyl-2,2,3,3-tetramethyl-4,7-dioxa-3,8-disiladecane (128). To a solution of carbinol **44** (6.0 g, 14 mmol, 1.0 equiv) and imidazole (1.4 g, 20 mmol, 1.5 equiv) in CH_2Cl_2 (14 mL, 1.0 M wrt **44**) at 0 °C was added chlorotriethylsilane (2.7 mL, 16 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C for 2 h, slowly warmed to rt over 2 h, stirred at rt for 7 h, quenched at 0 °C with sat. aq NH_4Cl (50 mL), and diluted with 1:1 hexanes/Et_2O (150 mL) and H_2O (10 mL). The layers were separated and the organic layer washed sequentially with sat. aq NH_4Cl and 1:1 H_2O/brine (50 mL each), dried over Na_2SO_4, filtered and concentrated. Column chromatography (gradient elution, 2% → 2.5% → 3% EtOAc in hexanes) afforded silyl ether **128** (7.4 g, 98% yield) as a clear, colorless oil. $[\alpha]_D^{24}$ –12.9° (*c* = 2.3, CH_2Cl_2); IR (neat) 3066, 3031, 2955, 2934, 2877, 1455, 1251, 1087, 1005, 961, 928, 836, 808, 777, 731, 697 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.37–7.27 (m, 10H, two of Ar**H**), 5.92 (ddd, *J* = 17.3, 10.4, 7.6 Hz, 1H, C_{31}-**H**), 5.30 (dd, *J* = 17.4, 0.8 Hz, 1H, one of C_{32}-**H**), 5.27 (m, *J* = 10.4 Hz, 1H, one of C_{32}-**H**), 4.77 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.68 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.63 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.38 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.13 (dd, *J* = 7.5, 5.0 Hz, 1H, C_{30}-**H**), 3.86 (ddd, *J* = 6.7, 4.4, 4.0 Hz, 1H, C_{28}-**H**), 3.79 (dd, *J* = 10.4, 3.8 Hz, 1H, one of C_{27}-**H**), 3.60 (dd, *J* = 10.4, 6.7 Hz, 1H, one of C_{27}-**H**), 3.49 (dd, *J* = 4.7, 4.7 Hz, 1H, C_{29}-**H**), 0.95 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.87 (s, 9H, C(C**H**$_3$)$_3$), 0.58 (q, *J* = 7.9 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.05 (s, 3H, one of SiC**H**$_3$), –0.01 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz,

$CDCl_3$) δ 138.9, 138.4, 136.4, 128.2, 128.1, 128.1, 128.1, 127.4, 127.4, 117.8, 82.3, 79.9, 74.2, 74.2, 70.7, 64.3, 25.9, 18.1, 6.8, 4.4 –4.1, –4.9; HRMS (ESI-TOF) *m/z* calcd for $C_{32}H_{52}NaO_4Si_2$ $[M+Na]^+$: 579.32963, found: 579.33115.



128 **45**

(2*S*,3*S*,4*S*)-2,3-Bis(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)-5-((triethylsilyl)oxy)pentanal (45). To a solution of alkene **128** (7.4 g, 13 mmol, 1.0 equiv) in 1:1 CH_2Cl_2/MeOH (0.27 L, 0.05 M wrt **128**) at –78 °C was added pyridine (11 mL, 0.13 mol, 10 equiv). The reaction mixture was bubbled with ozone until it turned blue, purged with oxygen until the color faded, quenched dropwise with a solution of triphenylphosphine (4.2 g, 16 mmol, 1.2 equiv) in 1:1 CH_2Cl_2/MeOH (66 mL, 0.24 M wrt PPh_3), slowly warmed to rt over 1.5 h, stirred at rt for 9 h, concentrated, and azeotroped with PhH (2 x 50 mL). Column chromatography (gradient elution, 2% → 3% → 4% EtOAc in hexanes) afforded aldehyde **45** (6.9 g, 94% yield) as a clear, colorless oil. $[\alpha]_D^{21}$ –25.6° (*c* = 3.0, CH_2Cl_2); IR (neat) 3065, 3032, 2954, 2933, 2878, 1733 (s), 1456, 1362, 1252, 1121, 1088, 1006, 959, 837, 779, 734, 698 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.68 (d, *J* = 1.8 Hz, 1H, C_{31}-**H**), 7.36–7.28 (m, 10H, Ar**H**), 4.72 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.65 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.63 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.55 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.09 (dd, *J* = 4.7, 1.2 Hz, 1H, C_{30}-**H**), 3.91 (ddd, *J* = 6.5, 5.3, 3.5 Hz, 1H, C_{28}-**H**), 3.83 (dd, *J* = 10.6, 3.5 Hz, 1H, one of C_{27}-**H**), 3.81 (dd, *J* = 5.3, 4.7 Hz, 1H, C_{29}-**H**), 3.67 (dd, *J* = 10.6, 6.5 Hz, 1H, one of C_{27}-**H**), 0.96 (t, *J* = 8.2 Hz, 9H, –$SiCH_2C$**H**$_3$), 0.86 (s, 9H, C(C**H**$_3$)$_3$), 0.59 (q, *J* = 8.2 Hz, 6H, –SiC**H**$_2CH_3$), 0.04 (s, 3H, one of SiC**H**$_3$), –0.01 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 202.0, 137.8, 137.2, 128.4, 128.33, 128.27, 128.1, 128.0, 127.8, 83.4, 80.1, 73.9, 73.25, 73.18, 63.6, 25.8, 18.0, 6.8, 4.3, –4.5, –5.0; HRMS (ESI-TOF) *m/z* calcd for $C_{31}H_{50}KO_5Si_2$ $[M+K]^+$: 597.28284, found: 597.28060.

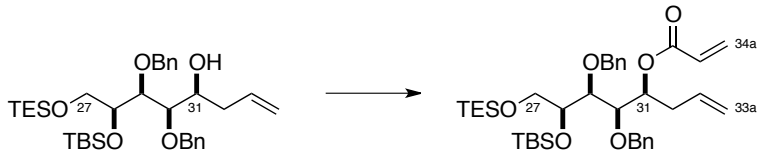


45 **46**

(4*S*,5*R*,6*S*,7*S*)-5,6-Bis(benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-8-((triethylsilyl)oxy)oct-1-en-4-ol (46). To a solution of aldehyde **45** (6.9 g, 12 mmol, 1.0 equiv) in CH_2Cl_2 (0.25 L, 0.05 M wrt **45**) at 0 °C was added a freshly prepared solution of $MgBr_2$•OEt_2 in 2:1 Et_2O/PhMe (74 mL, 0.67 M, 50 mmol, 4.0 equiv). The reaction mixture was stirred at 0 °C for 5 min, cooled to –78 °C, and then charged dropwise with a freshly prepared[60] solution of allylmagnesium bromide in Et_2O (44 mL, 0.42 M, 19 mmol, 1.5 equiv). The reaction mixture was stirred at –78 °C for 2 h, charged with additional allylmagnesium bromide (15 mL, 0.42 M in Et_2O, 6.2 mmol, 0.5 equiv), stirred at –78 °C for an additional 1.5 h, then briefly warmed to 0 °C and quenched with sat. aq NH_4Cl (100 mL). The biphasic mixture was diluted with H_2O (50 mL) and CH_2Cl_2 (50 mL) and warmed to rt. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was analyzed by ^{1}H-NMR spectroscopy to assess reaction diastereoselectivity (d.r. ≥ 95:05). Column chromatography (gradient elution, 3% → 4% → 5% EtOAc in hexanes) afforded homoallylic carbinol **46** (6.9 g, 92% yield) as a clear, colorless oil. $[\alpha]_D^{22}$ –11.8° (*c* = 1.4, CH_2Cl_2); IR (neat) 3452 (br), 3067, 3032, 2955, 2879, 1459, 1412, 1362, 1252, 1093, 1006, 917, 837, 808, 777, 733, 698 cm^{-1}; ^{1}H-NMR (600 MHz, C_6D_6) δ 7.32 (m, *J* = 7.6 Hz, 2H, two of Ar**H**), 7.28 (m, *J* = 7.6 Hz, 2H, two of Ar**H**), 7.16–7.13 (m, 4H, four of Ar**H**), 7.10–7.05 (m, *J* = 7.6, 7.1 Hz, 2H, two of Ar**H**), 5.94 (dddd, *J* = 17.0, 10.6, 7.7, 6.5 Hz, 1H, C_{33}-**H**), 5.07 (ddd, *J* = 15.9, 1.8, 1.1 Hz, 1H, one of C_{33a}-**H**), 5.05 (d, *J* = 10.5 Hz, 1H, one of C_{33a}-**H**), 4.88 (d, *J* = 11.2 Hz, 1H, one of –OC**H**$_2$Ph), 4.73 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.68 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.58 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.14 (ddd, *J* = 7.0, 4.1, 4.1 Hz, 1H, C_{28}-**H**), 4.04 (dd, *J* = 10.3, 4.1 Hz, 1H, one of C_{27}-**H**), 4.02 (dddd, *J* = 8.2, 6.5, 5.9, 2.3 Hz, 1H, C_{31}-**H**), 4.00 (dd, *J* = 7.3, 4.1 Hz, 1H, C_{29}-**H**), 3.84 (dd, *J* = 10.3, 7.1 Hz, 1H, one of C_{27}-**H**), 3.78 (dd, *J* = 7.3, 2.3 Hz, 1H, C_{30}-**H**), 2.44 (ddddd, *J* = 14.1, 6.5, 6.5, 1.8, 1.2 Hz, 1H, one

(60) Benson, R.E.; McKusick, B.C. *Org. Synth.* **1958**, *38*, 78–84.

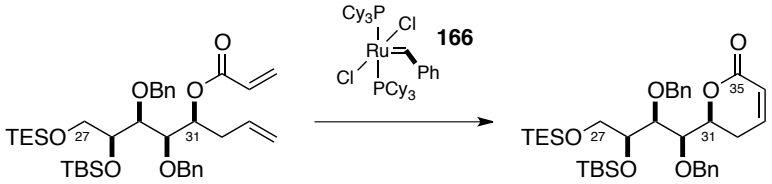
of C_{32}-**H**), 2.36 (ddddd, *J* = 14.1, 7.7, 6.4, 1.2, 1.2 Hz, 1H, one of C_{32}-**H**), 2.24 (d, *J* = 8.8 Hz, 1H, C_{28}-O**H**), 1.03 (s, 9H, C(C**H**$_3$)$_3$), 1.00 (t, *J* = 8.2 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.60 (q, *J* = 8.2 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.20 (s, 3H, one of SiC**H**$_3$), 0.13 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, C_6D_6) δ 139.3, 139.2, 135.9, 128.5, 128.3, 128.1, 127.9, 127.7, 117.1, 81.2, 80.8, 75.1, 74.8, 74.5, 71.2, 64.6, 39.7, 26.2, 18.5, 7.1, 4.8, –3.8, –4.5; HRMS (ESI-TOF) *m/z* calcd for $C_{34}H_{56}NaO_5Si_2$ [M+Na]$^+$: 623.35585, found: 623.35554.



46 **132**

(4*S*,5*R*,6*S*,7*S*)-5,6-Bis(benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-8-((triethylsilyl)oxy)oct-1-en-4-yl acrylate (132). To a solution of homoallylic carbinol **46** (1.2 g, 2.0 mmol, 1.0 equiv) in THF (9.8 mL, 0.2 M wrt **46**) at room temperature was added EtN(*i*Pr)$_2$ (1.4 mL, 7.8 mmol, 4.0 equiv), DMAP (60 mg, 0.49 mmol, 0.25 equiv), and a freshly prepared solution of acrylic pivalic anhydride in PhH (2.9 mL, 2.0 M, 5.9 mmol, 3.0 equiv). The resulting suspension was stirred at room temperature for 12 h, then charged with additional EtN(*i*Pr)$_2$ (1.4 mL, 7.8 mmol, 4.0 equiv), DMAP (60 mg, 0.49 mmol, 0.25 equiv), and acrylic pivalic anhydride (2.9 mL, 2.0 M, 5.9 mmol, 3.0 equiv). The reaction mixture was stirred for an additional 9 h, quenched with sat. aq $NaHCO_3$ (20 mL), and diluted with 1:1 hexanes/Et_2O (80 mL) and H_2O (5 mL). The layers were separated and the aqueous layer extracted with 1:1 hexanes/Et_2O (2 x 75 mL). The combined organic extracts were dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 1% → 1.5% EtOAc in hexanes) afforded acrylate ester **132** (1.3 g, 98% yield) as a clear, colorless oil. [α] $^{22}_{D}$ –17.4° (*c* = 2.3, CH_2Cl_2); IR (neat) 3066, 3032, 2954, 2880, 1726 (s), 1638, 1460, 1406, 1359, 1295, 1260, 1190, 1089, 1008, 921, 837, 807, 777, 734, 698 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.37–7.26 (m, 10H, Ar**H**), 6.41 (dd, *J* = 17.3, 1.5 Hz, 1H, one of C_{34a}-**H**), 6.16 (dd, *J* = 17.3, 10.2 Hz, 1H, C_{34}-**H**), 5.81 (dd, *J* = 10.2, 1.5 Hz, 1H, one of C_{34a}-**H**), 5.67 (dddd, *J* = 17.0, 10.0, 7.7, 7.0 Hz, 1H, C_{33}-**H**), 5.25 (ddd, *J* = 7.1, 5.3, 4.1 Hz, 1H, C_{31}-**H**), 5.00 (m, *J* = 1.2 Hz, 2H, C_{33a}-**H$_2$**), 4.79 (d, *J* = 11.2 Hz, 1H, one of –OC**H**$_2$Ph), 4.75 (d, *J* = 11.7 Hz, 1H,

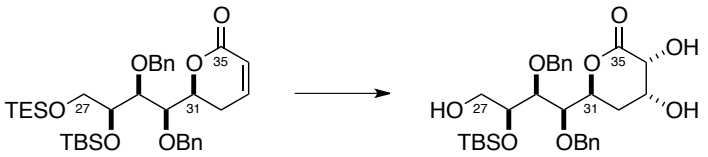
one of –OC**H**$_2$Ph), 4.72 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.67 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 3.92 (dd, *J* = 5.9, 4.1 Hz, 1H, C_{30}-**H**), 3.90 (ddd, *J* = 6.5, 5.3, 3.5 Hz, 1H, C_{28}-**H**), 3.77 (dd, *J* = 10.0, 5.3 Hz, 1H, one of C_{27}-**H**), 3.72 (dd, *J* = 5.9, 3.5 Hz, 1H, C_{29}-**H**), 3.55 (dd, *J* = 10.0, 6.5 Hz, 1H, one of C_{27}-**H**), 2.41–2.33 (m, *J* = 14.1, 7.6, 7.1, 7.0, 5.3, 1.1 Hz, 2H, C_{32}-**H$_2$**), 0.91 (s, 9H, C(C**H**$_3$)$_3$), 0.90 (t, *J* = 8.2 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.52 (q, *J* = 8.2 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.11 (s, 3H, one of SiC**H**$_3$), 0.09 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.6, 138.7, 138.4, 133.7, 130.8, 128.5, 128.3, 128.2, 127.9, 127.54, 127.47, 117.8, 78.7, 78.3, 74.6, 73.8, 73.3, 72.9, 63.7, 35.6, 26.0, 18.2, 6.8, 4.3, –3.9, –4.7; HRMS (ESI-TOF) *m/z* calcd for $C_{37}H_{59}O_6Si_2$ $[M+H]^+$: 655.3845, found: 655.3819.



132 **47**

(*S*)-6-((1*R*,2*S*,3*S*)-1,2-Bis(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-4-((triethylsilyl)oxy)butyl)-5,6-dihydro-2*H*-pyran-2-one (47). To a degassed solution of diene **132** (1.3 g, 1.9 mmol, 1.0 equiv) in PhH (0.13 L, 0.015 M wrt **132**) at room temperature was added ruthenium catalyst **166** (79 mg, 96 μmol, 0.05 equiv). The reaction mixture was purged with argon for 5 min, stirred at 65 °C for 8 h, then recharged with additional catalyst (79 mg, 96 μmol, 0.05 equiv) at this time and approximately every 12 h thrice after (total catalyst **166** added: 0.25 equiv). The reaction mixture was stirred at 65 °C for an additional 8 h, cooled to room temperature, concentrated to half volume, diluted with 9:1 hexanes/EtOAc (0.13 L) and filtered through a silica gel plug (4 cm). The filter cake was rinsed with 9:1 hexanes/EtOAc (0.5 L), and the filtrate concentrated. Column chromatography (gradient elution, 9:1 → 8:1 → 7:1 hexanes/EtOAc) afforded lactone **47** (0.83 g, 69% yield) as a pale brown oil contaminated with ruthenium-based impurities (<5%). A sufficient quantity of this material was repurified by column chromatography to produce a clear, colorless oil for characterization. $[\alpha]_D^{22}$ –59.8° (*c* = 2.3, CH_2Cl_2); IR (neat) 3064, 3032, 2954, 2885, 1733 (s), 1496, 1460, 1384, 1248, 1089, 957, 837, 813, 778, 738, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.36–7.26 (m, 10H, Ar**H**), 6.71 (ddd, *J* = 9.4, 6.4, 2.3 Hz, 1H, C_{33}-**H**), 5.95 (dd, *J* = 9.4, 2.3 Hz, 1H, C_{34}-**H**), 4.81 (d, *J* =

11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.77 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.71 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.70 (ddd, *J* = 12.9, 4.1, 4.1 Hz, 1H, C_{31}-**H**), 4.68 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 3.97 (ddd, *J* = 5.9, 4.1, 3.6 Hz, 1H, C_{28}-**H**), 3.86 (dd, *J* = 5.9, 4.1 Hz, 1H, C_{29}-**H**), 3.84 (dd, *J* = 5.9, 4.1 Hz, 1H, C_{30}-**H**), 3.74 (dd, *J* = 10.6, 3.5 Hz, 1H, one of C_{27}-**H**), 3.64 (dd, *J* = 10.6, 5.9 Hz, 1H, one of C_{27}-**H**), 2.39 (dddd, *J* = 18.2, 12.9, 2.4, 2.3 Hz, 1H, one of C_{32}-**H**), 1.82 (ddd, *J* = 18.2, 6.5, 4.1 Hz, 1H, one of C_{32}-**H**), 0.94 (t, *J* = 8.0 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.89 (s, 9H, C(C**H**$_3$)$_3$), 0.57 (q, *J* = 8.0 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.08 (s, 3H, one of SiC**H**$_3$), 0.05 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.8, 145.2, 138.3, 138.2, 128.4, 128.3, 128.2, 127.7, 127.6, 121.0, 78.6, 78.4, 78.2, 75.0, 73.7, 73.5, 64.1, 25.9, 25.8, 18.1, 6.8, 4.3, –4.3, –4.7; HRMS (ESI-TOF) *m/z* calcd for $C_{35}H_{55}O_6Si_2$ $[M+H]^+$: 627.3532, found: 627.3526.



47 **48**

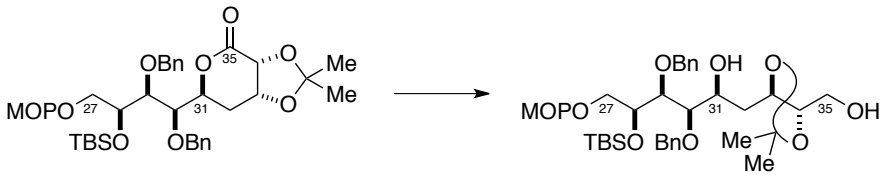
(3*R*,4*R*,6*S*)-6-((1*R*,2*S*,3*S*)-1,2-Bis(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-4-hydroxybutyl)-3,4-dihydroxytetrahydro-2*H*-pyran-2-one (48). To a bright yellow suspension of $NaIO_4$ (0.76 g, 3.5 mmol, 1.5 equiv) and $CeCl_3$•7H_2O (88 mg, 0.24 mmol, 0.1 equiv) in deionized H_2O (1.1 mL, 3⅓ M wrt $NaIO_4$) at 0 °C was added EtOAc (3.0 mL, 1.2 M wrt $NaIO_4$), MeCN (3.5 mL, 1.0 M wrt $NaIO_4$), and an aqueous solution of $RuCl_3$ (0.12 mL, 0.1 M, 12 μmol, 0.005 equiv). The bilayer suspension was stirred at 0 °C for 2 min, then charged slowly dropwise with a solution of unsaturated lactone **47** (1.5 g, 2.4 mmol, 1.0 equiv) in EtOAc (3.0 mL, 0.5 M overall wrt **47**) over 1 min (with 1.0 mL and 0.7 mL rinses). The reaction mixture was vigorously stirred at 0 °C for 40 min, charged with Na_2SO_4 (2.4 g), then filtered through Na_2SO_4 with EtOAc rinses (0.3 L total) into a separatory funnel containing sat. aq Na_2SO_3 (50 mL) and 1:1 H_2O/brine (100 mL). The layers were separated and the aqueous layer extracted with EtOAc (4 x 0.1 L). The combined organic extracts were dried over Na_2SO_4 with added hexanes (0.18 L) and filtered through a silica gel plug (4 cm). The filter cake was rinsed with 4:1 hexanes/EtOAc (0.25 L), then 1:2 hexanes/EtOAc (1 L), and the latter filtrate concentrated to afford crude triol **48** as a pale yellow solid contaminated

with aldehyde byproduct (~9%). $[\alpha]_D^{24}$ –0.06° (*c* = 2.3, CH_2Cl_2); IR (neat) 3444 (br), 3065, 3032, 2954, 2930, 2883, 2858, 1735 (s), 1497, 1455, 1390, 1362, 1253, 1200, 1115, 1048, 938, 837, 779, 735, 698 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.35–7.28 (m, 10H, Ar**H**), 5.07 (ddd, *J* = 11.7, 4.1, 1.7 Hz, 1H, C_{31}-**H**), 4.94 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.77 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.67 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.58 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.26 (m, 1H, C_{33}-**H**), 4.03 (m, *J* = 2.9 Hz, 1H, C_{34}-**H**), 3.99 (dd, *J* = 8.2, 4.1 Hz, 1H, C_{29}-**H**), 3.92 (ddd, *J* = 4.7, 4.1, 4.1 Hz, 1H, C_{28}-**H**), 3.77 (ddd, *J* = 11.1, 7.6, 3.5 Hz, 1H, one of C_{27}-**H**), 3.73 (dd, *J* = 8.2, 1.7 Hz, 1H, C_{30}-**H**), 3.71 (ddd, *J* = 11.1, 4.7, 4.7 Hz, 1H, one of C_{27}-**H**), 3.40 (s, 1H, C_{34}-O**H**), 2.64 (s, 1H, C_{33}-O**H**), 2.10 (dd, *J* = 7.6, 4.7 Hz, 1H, C_{27}-O**H**), 2.08 (dddd, *J* = 14.1, 11.7, 2.4, 2.3 Hz, 1H, one of C_{32}-**H**), 1.90 (ddd, *J* = 14.0, 4.1, 4.1 Hz, 1H, one of C_{32}-**H**), 0.88 (s, 9H, C(C**H**$_3$)$_3$), 0.06 (s, 6H, Si(C**H**$_3$)$_2$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.7, 138.1, 137.9, 128.4, 128.1, 128.0, 127.8, 127.7, 79.8, 79.4, 76.9, 75.3, 74.4, 72.1, 70.5, 66.1, 63.1, 30.0, 25.8, 18.0, –4.8, –4.9; HRMS (ESI-TOF) *m/z* calcd for $C_{29}H_{42}NaO_8Si$ $[M+Na]^+$: 569.2541, found: 569.2558.

48 **49**

(3a*R*,6*S*,7a*R*)-6-((1*R*,2*S*,3*S*)-1,2-Bis(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-4-((2-methoxypropan-2-yl)oxy)butyl)-2,2-dimethyldihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4(6*H*)-one (49). To a solution of crude triol **48** (theoretical 1.3 g, 2.4 mmol, 1.0 equiv) in 2:1 acetone/2,2-dimethoxypropane (47 mL, 0.05 M wrt **48**) at rt was added PPTS (59 mg, 0.24 mmol, 0.1 equiv). The reaction mixture was stirred at 35 °C for 12 h, quenched with $NaHCO_3$ (s) (~0.1 g), stirred vigorously for an additional 30 min at rt, and filtered through Celite®. The filter cake was rinsed with EtOAc (75 mL total), and the filtrate concentrated. Column chromatography (gradient elution, 18% → 20% → 25% EtOAc in hexanes) afforded acetonide **49** (1.0 g, 65% yield, two steps) as a clear, colorless oil. $[\alpha]_D^{24}$ +2.2° (*c* = 2.1, CH_2Cl_2); IR (neat) 3062, 3030, 2988, 2934, 2893, 2858, 1751 (s), 1459, 1377, 1261, 1211, 1156, 1114, 1077, 1049, 930, 834, 779, 738, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.35–

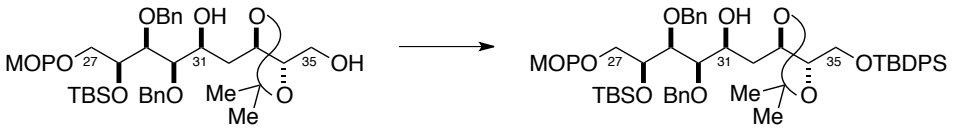
7.26 (m, 10H, Ar**H**), 4.92 (ddd, *J* = 10.6, 2.9, 2.4 Hz, 1H, C_{31}-**H**), 4.87 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.74 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.68 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.63 (d, *J* = 11.2 Hz, 1H, one of –OC**H**$_2$Ph), 4.55 (ddd, *J* = 7.0, 4.1, 3.5 Hz, 1H, C_{33}-**H**), 4.50 (d, *J* = 7.1 Hz, 1H, C_{34}-**H**), 4.01 (ddd, *J* = 6.4, 4.1, 3.5 Hz, 1H, C_{28}-**H**), 3.92 (dd, *J* = 7.1, 4.1 Hz, 1H, C_{29}-**H**), 3.80 (dd, *J* = 7.1, 2.9 Hz, 1H, C_{30}-**H**), 3.60 (dd, *J* = 10.0, 3.5 Hz, 1H, one of C_{27}-**H**), 3.50 (dd, *J* = 10.0, 6.5 Hz, 1H, one of C_{27}-**H**), 3.18 (s, 3H, –OC**H**$_3$), 2.01 (ddd, *J* = 14.6, 10.5, 4.1 Hz, 1H, one of C_{32}-**H**), 1.75 (ddd, *J* = 14.7, 2.9, 2.4 Hz, 1H, one of C_{32}-**H**), 1.46 (s, 3H, one of C**H**$_3$), 1.32 (s, 3H, one of C**H**$_3$), 1.31 (s, 6H, two of C**H**$_3$), 0.89 (s, 9H, C(C**H**$_3$)$_3$), 0.09 (s, 3H, one of Si(C**H**$_3$)$_2$), 0.05 (s, 3H, one of Si(C**H**$_3$)$_2$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.9, 138.4, 138.0, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 110.4, 99.9, 80.0, 79.3, 75.2, 74.8, 74.0, 72.8, 72.1, 71.5, 62.0, 48.6, 30.4, 26.1, 26.0, 24.42, 24.40, 23.8, 18.3, –4.3, –4.8; HRMS (ESI-TOF) *m/z* calcd for $C_{36}H_{54}NaO_9Si$ $[M+Na]^+$: 681.3429, found: 681.3412.



49 **50**

(2*S*,3*R*,4*S*,5*S*)-3,4-Bis(benzyloxy)-5-((*tert*-butyldimethylsilyl)oxy)-1-((4*R*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-((2-methoxypropan-2-yl)oxy)hexan-2-ol (50). To a solution of lactone **49** (1.0 g, 1.5 mmol, 1.0 equiv) in THF (15 mL, 0.10 M wrt **49**) at 0 °C was added H_2O (44 μL, 2.5 mmol, 1.6 equiv) and $LiBH_4$ (50 mg, 1.1 mmol, 1.5 equiv). The reaction mixture was slowly warmed to rt o/n (12 h total stir time), then recooled to 0 °C, quenched with 1 M aq NaOH (15 mL), stirred vigorously at rt for 1 h, and diluted with Et_2O (75 mL). The layers were separated and the organic layer washed sequentially with H_2O and brine (10 mL each). The combined aqueous layers were extracted with Et_2O (3 x 50 mL), and the combined organic extracts were dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 5:2 → 2:1 → 3:2 hexanes/EtOAc + 1% Et_3N) afforded diol **50** (0.92 g, 91% yield) as a clear, colorless oil. $[\alpha]_D^{23}$ –7.8° (*c* = 2.3, CH_2Cl_2); IR (neat) 3456 (br), 3060, 3029, 2987, 2934, 2883, 1460, 1374,

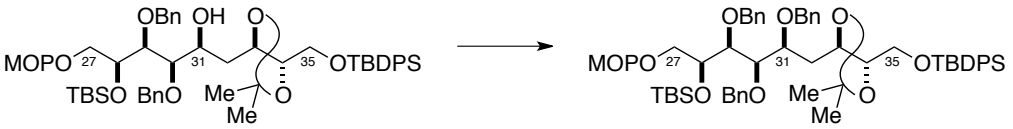
1252, 1215, 1078, 1051, 835, 778, 738, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.37–7.26 (m, 10H, Ar**H**), 4.84 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.75 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.68 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.62 (d, *J* = 11.2 Hz, 1H, one of –OC**H**$_2$Ph), 4.14 (ddd, *J* = 9.3, 5.9, 4.7 Hz, 1H, C_{33}-**H**), 4.03 (ddd, *J* = 7.1, 5.9, 4.7 Hz, 1H, C_{34}-**H**), 4.02 (ddd, *J* = 7.6, 4.1, 3.5 Hz, 1H, C_{28}-**H**), 3.98 (dddd, *J* = 8.8, 4.7, 4.1, 2.9 Hz, 1H, C_{31}-**H**), 3.82 (dd, *J* = 7.1, 4.1 Hz, 1H, C_{29}-**H**), 3.63 (dd, *J* = 10.0, 3.0 Hz, 1H, one of C_{27}-**H**), 3.62 (dd, *J* = 7.6, 2.9 Hz, 1H, C_{30}-**H**), 3.47 (ddd, *J* = 11.2, 7.1, 4.1 Hz, 1H, one of C_{35}-**H**), 3.44 (dd, *J* = 10.0, 7.6 Hz, 1H, one of C_{27}-**H**), 3.42 (ddd, *J* = 11.2, 7.6, 4.7 Hz, 1H, one of C_{35}-**H**), 3.17 (s, 3H, –OC**H**$_3$), 3.07 (d, *J* = 4.7 Hz, 1H, C_{31}-O**H**), 1.90 (dd, *J* = 7.6, 4.1 Hz, 1H, C_{35}-O**H**), 1.78 (ddd, *J* = 14.0, 9.4, 8.8 Hz, 1H, one of C_{32}-**H**), 1.49 (ddd, *J* = 14.1, 4.2, 4.1 Hz, 1H, one of C_{32}-**H**), 1.44 (s, 3H, one of C**H**$_3$), 1.32 (s, 3H, one of C**H**$_3$), 1.31 (s, 3H, one of C**H**$_3$), 1.30 (s, 3H, one of C**H**$_3$), 0.89 (s, 9H, C(C**H**$_3$)$_3$), 0.09 (s, 3H, one of Si(C**H**$_3$)$_2$), 0.04 (s, 3H, one of Si(C**H**$_3$)$_2$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.6, 138.4, 128.5, 128.31, 128.30, 128.0, 127.7, 127.6, 108.3, 99.9, 80.4, 80.0, 77.8, 75.6, 74.7, 73.9, 72.4, 69.8, 62.0, 61.5, 48.4, 32.3, 28.1, 25.9, 25.4, 24.4, 24.4, 18.2, –4.3, –4.8; HRMS (ESI-TOF) *m/z* calcd for $C_{36}H_{58}NaO_9Si$ $[M+Na]^+$: 685.3742, found: 685.3736.



50 **133**

(2*S*,3*R*,4*S*,5*S*)-3,4-Bis(benzyloxy)-5-((*tert*-butyldimethylsilyl)oxy)-1-((4*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-((2-methoxypropan-2-yl)oxy)hexan-2-ol (133). To a solution of diol **50** (1.7 g, 2.6 mmol, 1.0 equiv) and imidazole (0.26 g, 3.8 mmol, 1.5 equiv) in DMF (13 mL, 0.20 M wrt **50**) at 0 °C was added *tert*-butylchlorodiphenylsilane (0.80 mL, 3.1 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C for 6 h, quenched with sat. aq $NaHCO_3$ (25 mL), and diluted with 1:1 hexanes/Et_2O (0.1 L) and H_2O (15 mL). The layers were separated and the aqueous layer extracted with 1:1 hexanes/Et_2O (3 x 75 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Column chromatography (gradient elution, 9% → 10% → 12% EtOAc in hexanes) afforded silyl ether **133** (2.1 g, 92% yield) as a clear, colorless oil. $[\alpha]_D^{23}$ +0.21° (*c* =

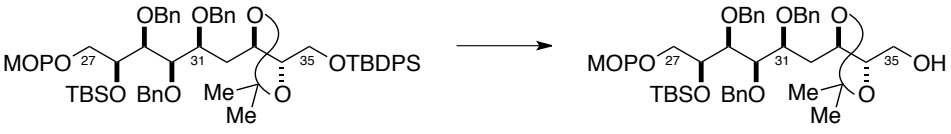
2.9, CH_2Cl_2); IR (neat) 3543 (br), 3062, 3031, 2990, 2932, 2888, 2857, 1468, 1430, 1370, 1251, 1214, 1112, 1082, 1056, 831, 777, 737, 701 cm^{-1}; ^{1}H-NMR (600 MHz, C_6D_6) δ 7.78–7.72 (m, *J* = 3.5 Hz, 4H, Ar**H**), 7.31 (m, *J* = 7.0, 5.3 Hz, 4H, Ar**H**), 7.21–7.18 (m, *J* = 6.5, 4.1 Hz, 6H, Ar**H**), 7.11 (m, *J* = 7.0, 1.2 Hz, 4H, Ar**H**), 7.04 (m, *J* = 7.6, 1.2 Hz, 2H, Ar**H**), 4.88 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.74 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.68 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.66 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.39 (dddd, *J* = 11.4, 4.7, 4.7, 2.9 Hz, 1H, C_{31}-**H**), 4.34 (ddd, *J* = 7.6, 3.5, 3.5 Hz, 1H, C_{34}-**H**), 4.20 (ddd, *J* = 8.2, 5.9, 2.3 Hz, 1H, C_{33}-**H**), 4.19–4.14 (m, *J* = 7.0, 5.9, 2.9 Hz, 2H, C_{28}-**H** and C_{29}-**H**), 3.97 (dd, *J* = 10.0, 3.5 Hz, 1H, one of C_{35}-**H**), 3.89 (dd, *J* = 7.0, 2.9 Hz, 1H, C_{30}-**H**), 3.81 (dd, *J* = 10.6, 5.9 Hz, 1H, one of C_{27}-**H**), 3.78 (dd, *J* = 11.1, 7.0 Hz, 1H, one of C_{27}-**H**), 3.73 (dd, *J* = 10.0, 7.6 Hz, 1H, one of C_{35}-**H**), 3.17 (d, *J* = 4.7 Hz, 1H, C_{31}-O**H**), 3.14 (s, 3H, –OC**H**$_3$), 2.13 (ddd, *J* = 14.1, 11.2, 8.2 Hz, 1H, one of C_{32}-**H**), 1.95 (ddd, *J* = 14.1, 4.7, 2.3 Hz, 1H, one of C_{32}-**H**), 1.34 (s, 3H, one of C**H**$_3$), 1.31 (s, 3H, one of C**H**$_3$), 1.29 (s, 3H, one of C**H**$_3$), 1.21 (s, 3H, one of C**H**$_3$), 1.13 (s, 9H, C(C**H**$_3$)$_3$), 1.08 (s, 9H, C(C**H**$_3$)$_3$), 0.24 (s, 3H, one of Si(C**H**$_3$)$_2$), 0.21 (s, 3H, one of Si(C**H**$_3$)$_2$); ^{13}C-NMR (125 MHz, C_6D_6) δ 139.5, 139.4, 136.0, 135.9, 133.8, 133.7, 130.1, 130.0, 128.5, 128.3, 128.14, 128.12, 128.09, 128.06, 127.9, 127.61, 127.59, 108.5, 100.1, 80.9, 80.5, 78.5, 77.0, 74.7, 74.4, 73.4, 70.9, 63.2, 62.9, 48.3, 33.2, 28.1, 27.1, 26.3, 25.6, 24.7, 24.6, 19.4, 18.6, –3.8, –4.4; HRMS (ESI-TOF) *m/z* calcd for $C_{52}H_{76}NaO_9Si_2$ $[M+Na]^+$: 923.4920, found: 923.4888.



133 **51**

(*S*)-3,3,8,8,9,9-Hexamethyl-6-((1*S*,2*R*,3*S*)-1,2,3-tris(benzyloxy)-4-((4*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)butyl)-2,4,7-trioxa-8-siladecane (51). To a solution of carbinol **133** (2.1 g, 2.3 mmol, 1.0 equiv) in DMF (12 mL, 0.20 M wrt **133**) at –20 °C was added sodium hydride (0.28 g, 60 wt% mineral oil dispersion, 7.0 mmol, 3.0 equiv). The suspension was stirred at –20 °C for 15 min, then charged with benzyl bromide (0.42 mL, 3.5 mmol, 1.5 equiv) and tetrabutylammonium iodide (86 mg, 0.23 mmol, 0.1 equiv). The reaction mixture was stirred between –20 °C and –5 °C for 6 h, briefly

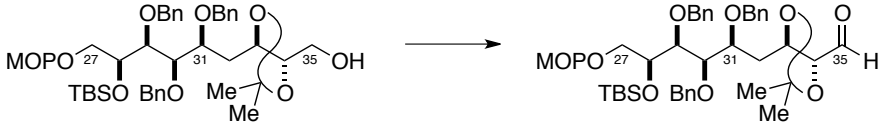
warmed to 0 °C, then quenched with sat. aq $NaHCO_3$ (50 mL), and diluted with 1:1 hexanes/Et_2O (0.15 L) and H_2O (50 mL). The layers were separated and the aqueous layer extracted with 1:1 hexanes/Et_2O (3 x 0.1 L). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Column chromatography (gradient elution, 6% → 8% → 9% EtOAc in hexanes) afforded benzyl ether **51** (2.1 g, 92% yield) as a clear, colorless oil. $[\alpha]_D^{25}$ –0.42° (*c* = 2.0, CH_2Cl_2); IR (neat) 3069, 3031, 2988, 2933, 2890, 2858, 1456, 1429, 1378, 1252, 1213, 1110, 1082, 1052, 832, 778, 736, 700 cm^{-1}; ^{1}H-NMR (600 MHz, C_6D_6) δ 7.83–7.79 (m, 4H, Ar**H**), 7.38 (m, *J* = 7.0 Hz, 2H, Ar**H**), 7.33 (m, *J* = 7.1 Hz, 2H, Ar**H**), 7.22–7.17 (m, 8H, Ar**H**), 7.16–7.02 (m, 15H, Ar**H**), 4.81 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.79 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.75 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.68 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.67 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.57 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.41 (ddd, *J* = 10.5, 5.8, 2.4 Hz, 1H, C_{33}-**H**), 4.30 (ddd, *J* = 7.6, 4.1, 3.5 Hz, 1H, C_{28}-**H**), 4.19 (ddd, *J* = 8.2, 4.1, 4.1 Hz, 1H, C_{31}-**H**), 4.17–4.13 (m, *J* = 4.7, 4.1, 4.1 Hz, 2H, C_{29}-**H** and C_{30}-**H**), 4.08 (ddd, *J* = 5.9, 5.8, 5.3 Hz, 1H, C_{34}-**H**), 4.01 (dd, *J* = 10.0, 3.6 Hz, 1H, one of C_{27}-**H**), 3.85 (dd, *J* = 10.6, 5.9 Hz, 1H, one of C_{35}-**H**), 3.79 (dd, *J* = 10.5, 5.3 Hz, 1H, one of C_{35}-**H**), 3.67 (dd, *J* = 10.0, 7.6 Hz, 1H, one of C_{27}-**H**), 3.08 (s, 3H, –OC**H**$_3$), 2.36 (ddd, *J* = 14.1, 8.2, 2.4 Hz, 1H, one of C_{32}-**H**), 2.18 (ddd, *J* = 14.1, 10.5, 3.5 Hz, 1H, one of C_{32}-**H**), 1.46 (s, 3H, one of C**H**$_3$), 1.28 (s, 3H, one of C**H**$_3$), 1.26 (s, 6H, two of C**H**$_3$), 1.16 (s, 9H, C(C**H**$_3$)$_3$), 1.07 (s, 9H, C(C**H**$_3$)$_3$), 0.25 (s, 3H, one of Si(C**H**$_3$)$_2$), 0.21 (s, 3H, one of Si(C**H**$_3$)$_2$); ^{13}C-NMR (125 MHz, C_6D_6) δ 139.5, 139.41, 139.38, 136.1, 136.0, 133.9, 133.8, 130.0, 128.5, 128.4, 128.3, 128.07, 128.06, 127.91, 127.86, 127.59, 127.56, 108.0, 100.0, 79.9, 78.7, 78.6, 76.8, 74.3, 74.0, 73.9, 73.1, 71.9, 63.6, 63.4, 48.3, 30.7, 28.4, 27.1, 26.4, 25.6, 24.62, 24.60, 19.5, 18.6, –3.7, –4.2; HRMS (ESI-TOF) *m/z* calcd for $C_{59}H_{82}NaO_9Si_2$ $[M+Na]^+$: 1013.5390, found: 1013.5355.



51 **134**

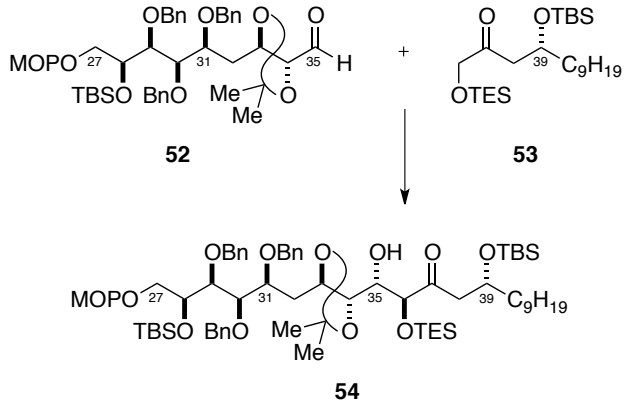
((4*S*,5*R*)-2,2-Dimethyl-5-((2*S*,3*R*,4*S*,5*S*)-2,3,4-tris(benzyloxy)-5-((*tert*-butyldimethylsilyl)oxy)-6-((2-methoxypropan-2-yl)oxy)hexyl)-1,3-dioxolan-4-yl)methanol

(134). To a solution of silyl ether **51** (0.70 g, 0.70 mmol, 1.0 equiv) in THF (14 mL, 0.05 M wrt **51**) at rt was added dropwise a pre-mixed solution of glacial acetic acid (40 μL, 0.70 mmol, 1.0 equiv) and tetrabutylammonium fluoride in THF (0.77 mL, 1.0 M, 0.77 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 15 h, quenched with sat. aq $NaHCO_3$ (15 mL), and diluted with 1:1 hexanes/Et_2O (40 mL) and H_2O (5 mL). The layers were separated and the aqueous layer extracted with 1:1 hexanes/Et_2O (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 20% → 22% → 24% EtOAc in hexanes + 1% Et_3N) afforded carbinol **134** (0.49 g, 93%) as a clear, colorless oil. $[\alpha]_D^{22}$ –12.5° (*c* = 1.8, CH_2Cl_2); IR (neat) 3468 (br), 3063, 3032, 2988, 2934, 2886, 2858, 1497, 1458, 1378, 1252, 1214, 1082, 1051, 964, 835, 778, 735, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.38–7.27 (m, 15H, Ar**H**), 4.74 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.71 (d, *J* = 12.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.69 (d, *J* = 11.2 Hz, 1H, one of –OC**H**$_2$Ph), 4.68 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.61 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.56 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.06 (ddd, *J* = 7.6, 4.7, 3.6 Hz, 1H, C_{28}-**H**), 3.95 (ddd, *J* = 9.4, 5.9, 4.1 Hz, 1H, C_{33}-**H**), 3.90 (dd, *J* = 4.7, 4.1 Hz, 1H, C_{30}-**H**), 3.84 (dd, *J* = 4.6, 4.2 Hz, 1H, C_{29}-**H**), 3.76 (m, *J* = 5.9, 5.8 Hz, 1H, C_{31}-**H**), 3.73 (m, *J* = 7.0, 4.1 Hz, 1H, C_{34}-**H**), 3.71 (dd, *J* = 10.0, 3.6 Hz, 1H, one of C_{27}-**H**), 3.39 (dd, *J* = 10.0, 7.6 Hz, 1H, one of C_{27}-**H**), 3.38 (m, *J* = 12.0, 7.1 Hz, 1H, one of C_{35}-**H**), 3.32 (br m, *J* = 10.5 Hz, 1H, one of C_{35}-**H**), 3.13 (s, 3H, –OC**H**$_3$), 1.81 (ddd, *J* = 14.1, 5.9, 4.1 Hz, 1H, one of C_{32}-**H**), 1.76 (br s, 1H, C_{35}-O**H**), 1.71 (ddd, *J* = 14.1, 9.4, 5.8 Hz, 1H, one of C_{32}-**H**), 1.43 (s, 3H, one of C**H**$_3$), 1.29 (s, 3H, one of C**H**$_3$), 1.25 (s, 6H, two of C**H**$_3$), 0.92 (s, 9H, C(C**H**$_3$)$_3$), 0.10 (s, 3H, one of Si(C**H**$_3$)$_2$), 0.06 (s, 3H, one of Si(C**H**$_3$)$_2$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.6, 138.41, 138.39, 128.5, 128.3, 128.2, 128.0, 127.9, 127.6, 127.54, 127.53, 107.9, 99.8, 78.8, 77.7, 77.5, 76.3, 74.0, 73.8, 73.3, 72.2, 72.0, 62.8, 61.6, 48.3, 30.0, 28.2, 26.0, 25.3, 24.39, 24.37, 18.2, –4.1, –4.6; HRMS (ESI-TOF) *m/z* calcd for $C_{43}H_{68}NO_9Si$ $[M+NH_4]^+$: 770.46579, found: 770.46677.



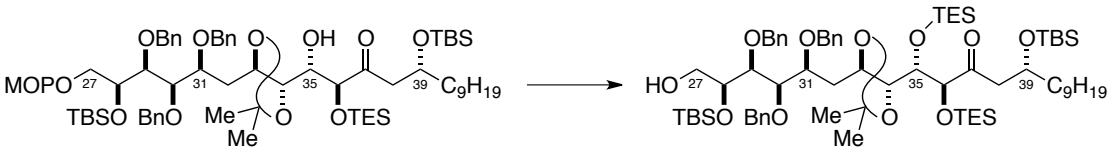
(4*R*,5*R*)-2,2-Dimethyl-5-((2*S*,3*R*,4*S*,5*S*)-2,3,4-tris(benzyloxy)-5-((*tert*-butyldimethylsilyl)oxy)-6-((2-methoxypropan-2-yl)oxy)hexyl)-1,3-dioxolane-4-carbaldehyde (52). To a solution of carbinol **134** (0.12 g, 0.16 mmol, 1.0 equiv) and EtN(*i*Pr)$_2$ (83 μL, 0.48 mmol, 3.0 equiv) in CH_2Cl_2 (0.46 mL, 0.35 M wrt **134**) and DMSO (80 μL, 2.0 M wrt **134**) at –30 °C was added a solution of SO_3•py (76 mg, 0.48 mmol, 3.0 equiv) in DMSO (0.37 mL, 1.3 M wrt SO_3•py). The reaction mixture was stirred between –30 °C and –20 °C for 1 h, then quenched with brine (8 mL), Et_2O (40 mL) and H_2O (2 mL). The layers were separated and the organic layer washed sequentially with 1 M aq $NaHSO_4$ (10 mL), sat. aq $NaHCO_3$ (10 mL), and 1:1 H_2O/brine (2 x 10 mL). The organic layer was then dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 15% → 20% EtOAc in hexanes) afforded aldehyde **52** (0.11 g, 94% yield) as a clear, colorless oil. $[\alpha]_D^{24}$ –12.0° (*c* = 2.6, CH_2Cl_2); IR (neat) 3067, 3031, 2989, 2934, 2887, 2857, 1734 (s), 1497, 1458, 1378, 1253, 1214, 1157, 1081, 1052, 963, 834, 778, 735, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.42 (d, *J* = 3.0 Hz, 1H, C_{35}-**H**), 7.39–7.27 (m, 15H, Ar**H**), 4.74 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.73 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.68 (d, *J* = 10.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.66 (d, *J* = 11.2 Hz, 1H, one of –OC**H**$_2$Ph), 4.62 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.54 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.18 (ddd, *J* = 8.8, 7.0, 4.1 Hz, 1H, C_{33}-**H**), 4.07 (ddd, *J* = 7.7, 4.7, 3.0 Hz, 1H, C_{28}-**H**), 3.88 (dd, *J* = 5.3, 3.5 Hz, 1H, C_{30}-**H**), 3.81 (ddd, *J* = 5.9, 5.9, 5.3 Hz, 1H, C_{31}-**H**), 3.78 (dd, *J* = 4.7, 3.5 Hz, 1H, C_{29}-**H**), 3.74 (dd, *J* = 7.0, 2.9 Hz, 1H, C_{34}-**H**), 3.73 (dd, *J* = 9.9, 2.9 Hz, 1H, one of C_{27}-**H**), 3.38 (dd, *J* = 10.0, 7.6 Hz, 1H, one of C_{27}-**H**), 3.14 (s, 3H, –OC**H**$_3$), 1.94 (ddd, *J* = 14.1, 5.9, 4.1 Hz, 1H, one of C_{32}-**H**), 1.21 (ddd, *J* = 14.7, 8.8, 5.9 Hz, 1H, one of C_{32}-**H**), 1.54 (s, 3H, one of C**H**$_3$), 1.30 (s, 3H, one of C**H**$_3$), 1.28 (s, 3H, one of C**H**$_3$), 1.26 (s, 3H, one of C**H**$_3$), 0.92 (s, 9H, C(C**H**$_3$)$_3$), 0.11 (s, 3H, one of Si(C**H**$_3$)$_2$), 0.06 (s, 3H, one of Si(C**H**$_3$)$_2$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 201.6, 138.5, 138.3, 138.2, 128.5, 128.3, 128.2, 128.10, 128.08, 127.62, 127.60, 127.56, 110.2, 99.8, 81.7, 78.6, 77.3, 75.51, 75.46, 73.7, 73.2, 72.2, 71.8, 62.9, 48.3, 30.9, 27.6, 26.0, 25.2, 24.4 (2C), 18.1, –4.2, –4.6; HRMS (ESI-TOF) *m/z* calcd for $C_{43}H_{62}NaO_9Si$ [M+Na]$^+$: 773.4055, found: 773.4047.

Synthesis of the C27–C48 Aldehyde



(5*S*,8*R*)-5-((*S*)-((4*S*,5*R*)-2,2-Dimethyl-5-((2*S*,3*R*,4*S*,5*S*)-2,3,4-tris(benzyloxy)-5-((*tert*-butyldimethylsilyl)oxy)-6-((2-methoxypropan-2-yl)oxy)hexyl)-1,3-dioxolan-4-yl)(hydroxy)methyl)-3,3-diethyl-10,10,11,11-tetramethyl-8-nonyl-4,9-dioxa-3,10-disiladodecan-6-one (54). To a solution of ketone **53** (0.12 g, 0.27 mmol, 2.1 equiv) and $EtNMe_2$ (58 μL, 0.53 mmol, 4.2 equiv) in pentane (1.3 mL, 0.2 M wrt **53**) at 0 °C was added Cy_2BCl (61 μL, 0.28 mmol, 2.2 equiv). The enolization mixture was stirred at 0 °C for 20 min, then stirred at rt for 16 h, then cooled to –78 °C and charged slowly dropwise with a solution of aldehyde **52** (0.11 g, 0.15 mmol, 1.0 equiv) in Et_2O (0.24 mL, 0.3 M wrt **52**) over 1 min (with 0.20 mL rinse). The reaction mixture was stirred at –78 °C for 45 min, slowly warmed to –40 °C over 0.5 h, stirred at –40 °C for 4 h, slowly warmed to –25 °C over 2 h, stirred at –25 °C for 10 h, then quenched at 0 °C with aq pH 7 buffer (3 mL), MeOH (3 mL), Et_2O (30 mL) and 30% aq H_2O_2 (1 mL). The biphasic mixture was stirred vigorously at 0 °C for 1 h, then at rt for 1 h. The layers were separated and the aqueous layer extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with 10% aq $Na_2S_2O_3$ (2 x 15 mL) and brine (15 mL), dried over Na_2SO_4 with added hexanes, filtered and concentrated. The residue was analyzed by ^{1}H-NMR spectroscopy to assess reaction diastereoselectivity (d.r. = 85:15). Column chromatography (gradient elution, 3% → 4% → 5% EtOAc in hexanes) afforded aldol adduct **54** (0.10 g, 57% yield) as a clear, colorless oil. $[\alpha]_D^{23}$ –7.6° (*c* = 2.3, CH_2Cl_2); IR (neat) 3558 (br), 3064, 3031, 2954, 2929, 2856, 1721 (s), 1497, 1467, 1379, 1253, 1212, 1086, 1052, 1004, 967, 835, 776, 732, 697 cm^{-1}; ^{1}H-NMR (600 MHz, C_6D_6) δ 7.41 (m, *J* = 8.2 Hz, 2H, two of Ar**H**), 7.39 (m, *J* = 7.7 Hz, 2H, two of Ar**H**), 7.36 (m, *J* =

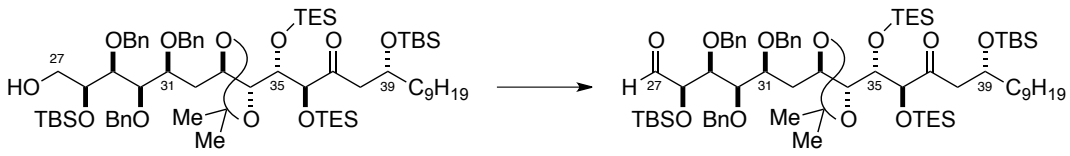
7.6 Hz, 2H, two of Ar**H**), 7.24–7.18 (m, 6H, six of Ar**H**), 7.13–7.09 (m, 3H, three of Ar**H**), 4.82 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.79 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.78 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.73 (d, *J* = 11.8 Hz, 1H, one of –OC**H**$_2$Ph), 4.65 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.58 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.54 (dddd, *J* = 6.5, 5.9, 5.3, 5.2 Hz, 1H, C_{39}-**H**), 4.49 (ddd, *J* = 10.0, 7.1, 2.9 Hz, 1H, C_{33}-**H**), 4.31 (m, *J* = 7.0 Hz, 1H, C_{34}-**H**), 4.30 (ddd, *J* = 7.6, 3.5, 3.0 Hz, 1H, C_{28}-**H**), 4.25 (d, *J* = 8.2 Hz, 1H, C_{36}-**H**), 4.15–4.13 (m, *J* = 6.5, 5.3, 4.7 Hz, 2H, C_{30}-**H** and C_{31}-**H**), 4.10 (dd, *J* = 4.7, 3.5 Hz, 1H, C_{29}-**H**), 4.01 (dd, *J* = 9.9, 3.0 Hz, 1H, one of C_{27}-**H**), 3.85 (dd, *J* = 8.8, 8.2 Hz, 1H, C_{35}-**H**), 3.66 (dd, *J* = 10.0, 7.6 Hz, 1H, one of C_{27}-**H**), 3.21 (dd, *J* = 18.2, 5.3 Hz, 1H, one of C_{38}-**H**), 3.08 (s, 3H, –OC**H**$_3$), 2.89 (dd, *J* = 18.2, 6.5 Hz, 1H, one of C_{38}-**H**), 2.53 (d, *J* = 8.8 Hz, 1H, C_{35}-O**H**), 2.50 (ddd, *J* = 14.1, 10.0, 4.1 Hz, 1H, one of C_{32}-**H**), 2.36 (ddd, *J* = 14.1, 6.5, 2.9 Hz, 1H, one of C_{32}-**H**), 1.82–1.76 (m, *J* = 13.5, 5.9, 4.7 Hz, 1H, one of C_{40}-**H**), 1.65–1.60 (m, *J* = 13.5, 5.9, 5.3 Hz, 1H, one of C_{40}-**H**), 1.57–1.45 (m, 2H, C_{41}-**H**$_2$), 1.38 (s, 3H, one of C**H**$_3$), 1.37–1.22 (m, 12H, $C_{42–47}$-**H**$_2$), 1.263 (s, 3H, one of C**H**$_3$), 1.257 (s, 3H, one of C**H**$_3$), 1.22 (s, 3H, one of C**H**$_3$), 1.07 (s, 9H, C(C**H**$_3$)$_3$), 1.02 (s, 9H, C(C**H**$_3$)$_3$), 1.01 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.90 (t, *J* = 7.1 Hz, 3H, C_{48}-**H**$_3$), 0.67 (q, *J* = 7.8 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.25 (s, 3H, one of SiC**H**$_3$), 0.22 (s, 3H, one of SiC**H**$_3$), 0.20 (s, 3H, one of SiC**H**$_3$), 0.18 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, C_6D_6) δ 209.2, 139.3 (3C), 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.64, 127.59, 107.9, 100.0, 79.8, 79.4, 78.7, 76.9, 75.7, 74.5, 74.1, 73.9, 72.9, 72.1, 72.0, 68.3, 63.4, 48.2, 46.4, 38.0, 32.3, 31.1, 30.2, 30.1, 30.0, 29.7, 27.0, 26.4, 26.2, 25.5, 24.62, 24.60, 24.56, 23.1, 18.5, 18.3, 14.3, 7.0, 5.1, –3.8, –4.20, –4.21, –4.5; HRMS (ESI-TOF) *m/z* calcd for $C_{68}H_{120}NaO_{12}Si_3$ $[M+NH_4]^+$: 1226.81128, found: 1226.81179.



54 **135**

(5*R*,8*S*,9*S*)-9-((4*R*,5*R*)-2,2-Dimethyl-5-((2*S*,3*R*,4*S*,5*S*)-2,3,4-tris(benzyloxy)-5-((*tert*-butyldimethylsilyl)oxy)-6-hydroxyhexyl)-1,3-dioxolan-4-yl)-11,11-diethyl-2,2,3,3-tetramethyl-5-nonyl-8-((triethylsilyl)oxy)-4,10-dioxa-3,11-disilatridecan-7-one (135). To a solution of carbinol **54** (0.10 g, 83 μmol, 1.0 equiv) and 2,6-lutidine (39 μL, 0.33 mmol, 4.0

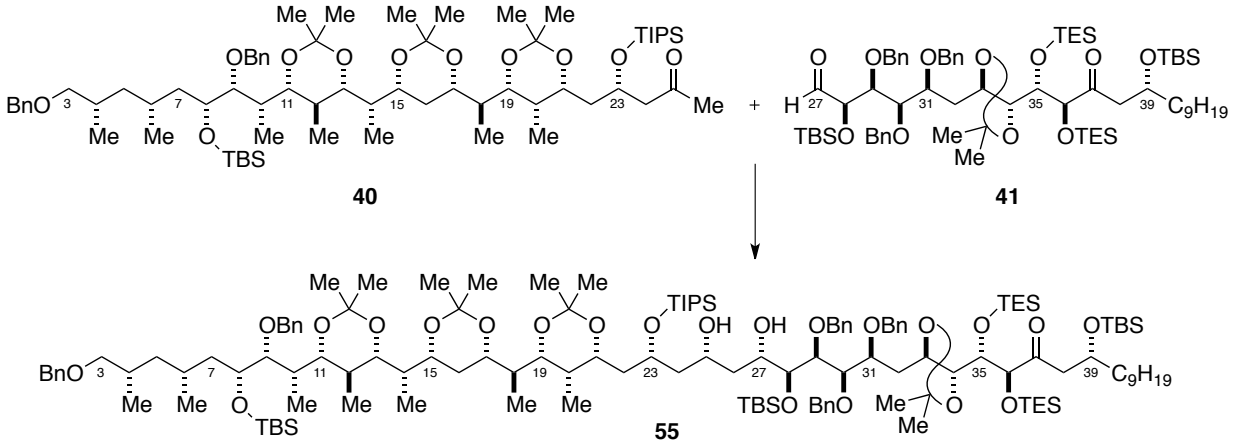
equiv) in CH_2Cl_2 (0.41 mL, 0.2 M wrt **54**) at 0 °C was added TESOTf (28 μL, 0.12 mmol, 1.5 equiv). The reaction mixture was stirred between 0 °C and 10 °C for 3 h, charged with additional TESOTf (19 μL, 83 μmol, 1.0 equiv), stirred between 0 °C and 10 °C for 1 h, then quenched with 1 M aq H_2SO_4 (1 mL) and Et_2O (2 mL). The biphasic mixture was stirred vigorously at 0 °C for 1 h, then diluted with H_2SO_4 (6 mL) and Et_2O (40 mL), and the layers were separated. The organic layer was washed sequentially with sat. aq $NaHCO_3$ and brine (6 mL each), dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 3% → 4% EtOAc in hexanes) afforded diol **135** (86 mg, 83% yield) as a clear, colorless oil. $[\alpha]_D^{25}$ +19.6° (*c* = 1.8, CH_2Cl_2); IR (neat) 3510 (br), 3065, 3031, 2930, 2857, 1711 (s), 1461, 1408, 1378, 1252, 1219, 1098, 1061, 1008, 836, 776, 732, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.32–7.20 (m, 15H, Ar**H**), 4.80 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.66 (m, 2H, –OC**H**$_2$Ph), 4.63 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.56 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.50 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.28 (ddd, *J* = 11.1, 5.0, 3.1 Hz, 1H, C_{33}-**H**), 4.22 (dddd, *J* = 6.0, 5.7, 5.6, 5.4 Hz, 1H, C_{39}-**H**), 3.98 (ddd, *J* = 4.1, 4.0, 3.5 Hz, 1H, C_{31}-**H**), 3.92 (dd, *J* = 4.4, 4.0 Hz, 1H, C_{30}-**H**), 3.91 (dd, *J* = 6.0, 5.0 Hz, 1H, C_{29}-**H**), 3.84 (m, *J* = 5.3, 5.0 Hz, 1H, C_{28}-**H**), 3.84 (dd, *J* = 8.8, 5.0 Hz, 1H, C_{34}-**H**), 3.77 (dd, *J* = 8.9, 1.9 Hz, 1H, C_{35}-**H**), 3.69 (ddd, *J* = 11.3, 8.2, 3.1 Hz, 1H, one of C_{27}-**H**), 3.67 (d, *J* = 1.9 Hz, 1H, C_{36}-**H**), 3.56 (ddd, *J* = 11.4, 5.1, 4.7 Hz, 1H, one of C_{27}-**H**), 2.89 (dd, *J* = 19.6, 6.7 Hz, 1H, one of C_{38}-**H**), 2.82 (dd, *J* = 19.6, 5.3 Hz, 1H, one of C_{38}-**H**), 1.78 (dd, *J* = 8.1, 4.7 Hz, 1H, C_{27}-O**H**), 1.75 (ddd, *J* = 13.0, 11.1, 4.2 Hz, 1H, one of C_{32}-**H**), 1.71 (m, *J* = 13.0, 2.8 Hz, 1H, one of C_{32}-**H**), 1.48–1.22 (m, 16H, $C_{40–47}$-**H**$_2$), 1.42 (s, 3H, one of C**H**$_3$), 1.26 (s, 3H, one of C**H**$_3$), 0.97 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.89 (s, 9H, one of C(C**H**$_3$)$_3$), 0.88 (t, 3H, C_{48}-**H**$_3$), 0.87 (s, 9H, one of C(C**H**$_3$)$_3$), 0.84 (t, *J* = 8.0 Hz, 9H, –SiCH$_2$C**H**$_3$), 0.70–0.57 (m, *J* = 7.8, 7.5, 7.3 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.43 (q, *J* = 7.9 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.08 (s, 3H, one of SiC**H**$_3$), 0.04 (s, 3H, one of SiC**H**$_3$), 0.01 (s, 3H, one of SiC**H**$_3$), –0.01 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.9, 138.8, 138.6, 138.3, 128.4, 128.2, 128.2, 128.2, 128.0, 127.5, 127.4, 127.4, 127.3, 107.7, 78.8, 78.6, 78.5, 77.5, 76.1, 75.3, 74.1, 73.9, 73.5, 73.3, 71.4, 67.3, 64.2, 48.7, 37.9, 31.9, 30.4, 29.8, 29.6, 29.6, 29.3, 28.7, 26.0, 25.9, 25.9, 25.2, 22.7, 18.1, 18.0, 14.1, 6.9, 6.8, 5.3, 5.1, 5.0, 4.5, –4.5, –4.5, –4.7, –4.7; HRMS (ESI-TOF) *m/z* calcd for $C_{70}H_{122}NaO_{11}Si_4$ $[M+Na]^+$: 1273.7956, found: 1273.7948.



(2*R*,3*S*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-6-((4*R*,5*R*)-5-((5*S*,6*S*,9*R*)-3,3-diethyl-11,11,12,12-tetramethyl-9-nonyl-7-oxo-6-((triethylsilyl)oxy)-4,10-dioxa-3,11-disilatridecan-5-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)hexanal (41). To a solution of carbinol **135** (0.24 g, 0.19 mmol, 1.0 equiv) and EtN(*i*Pr)$_2$ (0.10 mL, 0.58 mmol, 3.0 equiv) in CH_2Cl_2 (0.55 mL, 0.35 M wrt **135**) and DMSO (0.11 mL, 1.8 M wrt **135**) at –30 °C was added a solution of SO_3•py (0.092 g, 0.58 mmol, 3.0 equiv) in DMSO (0.44 mL, 1.3 M wrt SO_3•py). The reaction mixture was stirred between –30 °C and –20 °C for 1.5 h, quenched with brine (15 mL), then diluted with Et_2O (40 mL) and H_2O (1 mL). The layers were separated and the organic layer washed sequentially with 1 M aq $NaHSO_4$ (15 mL), sat. aq $NaHCO_3$ (15 mL), and 1:1 H_2O/brine (2 x 15 mL). The organic layer was then dried over Na_2SO_4 with added hexanes, filtered and concentrated. Column chromatography (gradient elution, 1% → 1.5% → 2% EtOAc in hexanes) afforded aldehyde **41** (0.23 g, 95% yield) as a clear, colorless oil. $[\alpha]_D^{26}$ +11.9° (*c* = 2.2, CH_2Cl_2); IR (neat) 3066, 3031, 2927, 2872, 1731 (s), 1714 (s), 1455, 1416, 1380, 1252, 1220, 1143, 1097, 1061, 1026, 979, 950, 894, 837, 777, 729, 699 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.74 (s, 1H, C_{27}-**H**), 7.33–7.18 (m, 15H, Ar**H**), 4.68 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.63 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.61 (d, *J* = 11.6 Hz, 1H, one of –OC**H**$_2$Ph), 4.47 (d, *J* = 11.4 Hz, 1H, one of –OC**H**$_2$Ph), 4.46 (d, *J* = 11.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.32 (d, *J* = 11.1 Hz, 1H, one of –OC**H**$_2$Ph), 4.25 (dddd, *J* = 5.7, 5.7, 5.7, 5.7 Hz, 1H, C_{39}-**H**), 4.22 (ddd, *J* = 11.4, 5.0, 2.1 Hz, 1H, C_{33}-**H**), 4.08 (dd, *J* = 5.9, 3.7 Hz, 1H, C_{29}-**H**), 3.97 (d, *J* = 5.7 Hz, 1H, C_{28}-**H**), 3.88 (dd, *J* = 5.6, 3.7 Hz, 1H, C_{30}-**H**), 3.84 (dd, *J* = 9.1, 5.1 Hz, 1H, C_{34}-**H**), 3.79 (m, 1H, C_{31}-**H**), 3.78 (dd, *J* = 9.1, 2.0 Hz, 1H, C_{35}-**H**), 3.70 (d, *J* = 2.1 Hz, 1H, C_{36}-**H**), 2.90 (dd, *J* = 19.6, 6.4 Hz, 1H, one of C_{38}-**H**), 2.85 (dd, *J* = 19.6, 5.6 Hz, 1H, one of C_{38}-**H**), 1.87 (ddd, *J* = 13.9, 3.7, 1.6 Hz, 1H, one of C_{32}-**H**), 1.75 (ddd, *J* = 13.8, 11.9, 5.0 Hz, 1H, one of C_{32}-**H**), 1.48–1.27 (m, 16H, $C_{40–47}$-**H$_2$**), 1.41 (s, 3H, one of C**H**$_3$), 1.27 (s, 3H, one of C**H**$_3$), 0.97 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H$_3$**), 0.89 (t, *J* = 7.0 Hz, 3H, C_{48}-**H$_3$**), 0.88 (s, 9H, one of C(C**H**$_3$)$_3$), 0.88 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H$_3$**), 0.88 (s,

9H, one of C(C**H**$_3$)$_3$), 0.71–0.59 (m, *J* = 8.1, 7.9, 7.8 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.43 (q, *J* = 7.9 Hz, 6H, –SiC**H**$_2$CH$_3$), 0.09 (s, 3H, one of SiC**H**$_3$), 0.06 (s, 3H, one of SiC**H**$_3$), 0.02 (s, 3H, one of SiC**H**$_3$), –0.10 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.9, 200.6, 138.7, 138.0, 137.7, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.7, 127.5, 127.4, 107.6, 80.9, 78.8, 78.4, 77.0, 76.9, 76.7, 75.3, 74.9, 73.7, 73.7, 72.1, 67.3, 48.7, 37.9, 31.9, 31.0, 29.8, 29.6, 29.6, 29.3, 28.6, 26.1, 25.9, 25.8, 25.2, 22.7, 18.3, 18.0, 14.1, 6.9, 6.8, 5.1, 4.5, –4.5, –4.6, –4.7, –5.5; HRMS (ESI-TOF) *m/z* calcd for $C_{70}H_{120}NaO_{11}Si_4$ [M+Na]$^+$: 1271.7800, found: 1271.7846.

Synthesis of Aflastatin A

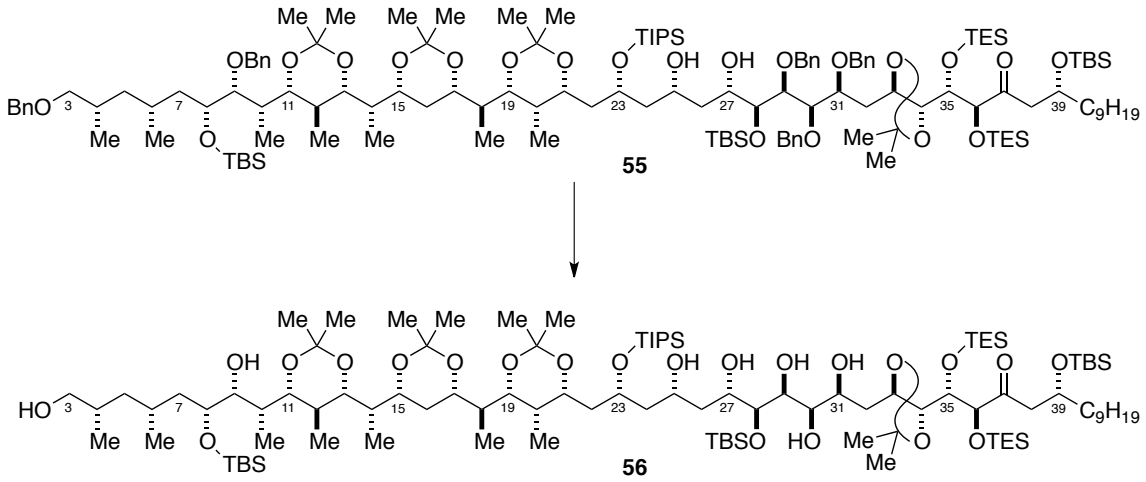


(5*R*,8*S*,9*S*)-9-((4*R*,5*R*)-2,2-Dimethyl-5-((2*S*,3*R*,4*S*,5*S*,6*S*,8*R*,10*R*)-2,3,4-tris(benzyloxy)-11-((4*R*,5*S*,6*S*)-6-((*S*)-1-((4*S*,6*R*)-6-((*S*)-1-((4*R*,5*R*,6*R*)-6-((2*S*,3*R*,4*R*,6*R*,8*S*)-3,9-bis(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)-6,8-dimethylnonan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-5-((*tert*-butyldimethylsilyl)oxy)-6,8-dihydroxy-10-((triisopropylsilyl)oxy)undecyl)-1,3-dioxolan-4-yl)-11,11-diethyl-2,2,3,3-tetramethyl-5-nonyl-8-((triethylsilyl)oxy)-4,10-dioxa-3,11-disilatridecan-7-one (55). To a solution of aldehyde **41** (0.23 g, 0.18 mmol, 1.0 equiv) and ketone **40** (0.24 g, 0.20 mmol, 1.1 equiv) in CH_2Cl_2 (1.3 mL, 0.14 M wrt **41**) at –5 °C was added freshly prepared $MgBr_2$•OEt_2 (0.38 g, 1.5 mmol, 8.0 equiv). The resulting suspension was stirred at –5 °C for 10 min, then charged dropwise with 1,2,2,6,6-pentamethylpiperidine (83 μL, 0.46 mmol, 2.5 equiv). The reaction mixture was stirred at –5 °C for 7 min, then

rapidly quenched with pre-chilled sat. aq $NaHCO_3$ (3 mL). The biphasic mixture was stirred vigorously at rt for 10 min, then diluted with Et_2O (30 mL), H_2O (10 mL) and sat. aq $NaHCO_3$ (15 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed sequentially with sat. aq NH_4Cl (2 x 20 mL) and brine (15 mL), dried over Na_2SO_4, filtered, concentrated and azeotroped with PhH (2 x 2 mL) to afford crude aldol adduct **163** as a clear, pale yellow oil that was used without further purification.

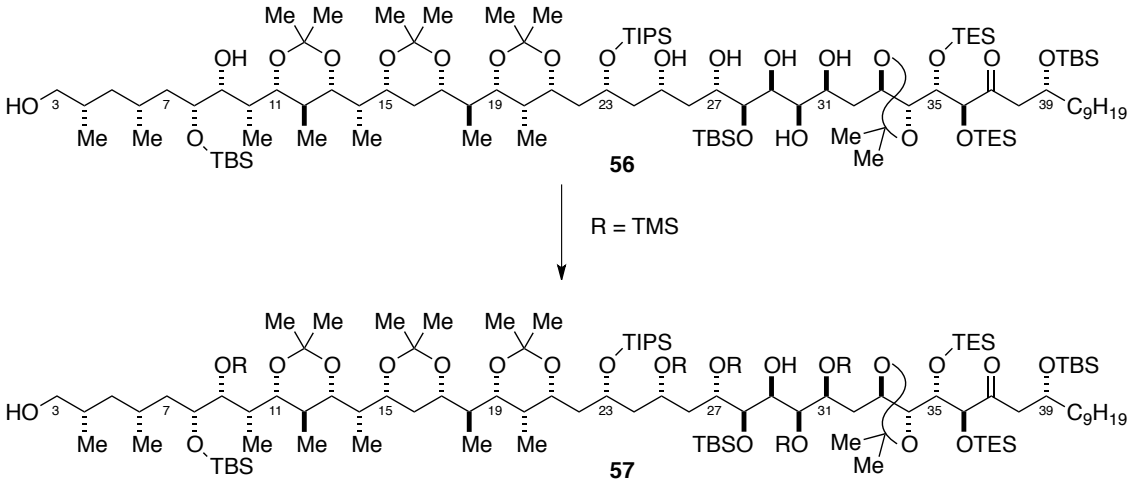
To a solution of crude aldol adduct **163** (theoretical 0.44 g, 0.18 mmol, 1.0 equiv) in 4:1 THF/MeOH (1.8 mL, 0.1 M wrt **163**) at –78 °C was added dropwise a solution of diethylmethoxyborane in THF (0.20 mL, 1.0 M, 0.20 mmol, 1.1 equiv). The reaction mixture was stirred at –78 °C for 2.5 h, then charged with sodium borohydride (21 mg, 0.55 mmol, 3.0 equiv) in one portion. The reaction mixture was slowly warmed to –55 °C over 0.5 h, stirred at –55 °C for 20 h, quenched with a pre-mixed mixture of 1 M aq NaOH (1 mL) and 30% aq H_2O_2 (0.4 mL), then diluted with 4:1 THF/MeOH (1 mL). The heterogeneous mixture was stirred vigorously at 0 °C for 1.5 h, then diluted with Et_2O (30 mL) and aq pH 7 buffer (3 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with 10% aq $Na_2S_2O_3$ (2 x 10 mL) and brine (10 mL), dried over Na_2SO_4 with added hexanes, filtered and concentrated. The residue was analyzed by ^{1}H-NMR spectroscopy to assess reaction diastereoselectivity (d.r. ≥ 95:05). Column chromatography (gradient elution, 6% → 6.5% EtOAc in hexanes) afforded diol **55** (0.31 g, 70% yield, two steps) as a white foam. $[\alpha]_D^{25}$ +1.0° (*c* = 1.2, CH_2Cl_2); IR (neat) 3498 (br), 3068, 3036, 2932, 2864, 1712, 1459, 1380, 1253, 1202, 1175, 1098, 1008, 982, 837, 775, 733, 698 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.34–7.21 (m, 25H, Ar**H**), 4.73 (d, *J* = 12.0 Hz, 1H, one of –OC**H**$_2$Ph), 4.70 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.70 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.66 (m, 2H, –OC**H**$_2$Ph), 4.61 (d, *J* = 11.7 Hz, 1H, one of –OC**H**$_2$Ph), 4.52 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.49 (d, *J* = 11.9 Hz, 1H, one of –OC**H**$_2$Ph), 4.45 (m, 2H, –OC**H**$_2$Ph), 4.28 (ddd, *J* = 11.6, 7.0, 2.5 Hz, 1H, C_{33}-**H**), 4.25 (m, *J* = 7.0, 6.0 Hz, 1H), 4.22 (m, 1H), 4.21 (m, *J* = 5.1, 5.1 Hz, 1H, C_{39}-**H**), 4.18–4.16 (m, 2H), 4.03–3.98 (m, 2H), 3.98–3.92 (m, 3H), 3.91 (m, 1H, C_{31}-**H**), 3.88 (m, 1H, C_8-**H**), 3.82 (dd, *J* = 8.9, 4.9 Hz, 1H, C_{34}-**H**), 3.79 (dd, *J* = 8.9, 1.9 Hz, 1H, C_{35}-**H**), 3.69 (m, 1H), 3.66 (d, *J* = 1.9 Hz, 1H, C_{36}-**H**), 3.60 (m, *J* =

1.6 Hz, 1H), 3.59 (m, *J* = 9.8 Hz, 1H), 3.54 (m, *J* = 7.2, 2.8 Hz, 2H), 3.40 (dd, *J* = 6.2, 2.6 Hz, 1H, C_9-**H**), 3.33 (dd, *J* = 9.1, 5.3 Hz, 1H, one of C_3-**H**), 3.14 (dd, *J* = 9.1, 7.4 Hz, 1H, one of C_3-**H**), 2.88 (dd, *J* = 19.6, 6.6 Hz, 1H, one of C_{38}-**H**), 2.83 (dd, *J* = 19.5, 5.4 Hz, 1H, one of C_{38}-**H**), 2.39 (m, *J* = 6.8, 6.6, 2.5 Hz, 1H, C_{10}-**H**), 1.94–1.80 (m, 4H), 1.80–1.57 (m, 8H), 1.52 (m, *J* = 1.9 Hz, 1H), 1.48–1.20 (m, 16H, $C_{40–47}$-**H_2**), 1.48–1.20 (m, 5H), 1.44 (s, 3H, one of C**H_3**), 1.39 (s, 3H, one of C**H_3**), 1.37 (s, 3H, one of C**H_3**), 1.37 (s, 3H, one of C**H_3**), 1.37 (s, 3H, one of C**H_3**), 1.35 (s, 3H, one of C**H_3**), 1.31 (s, 3H, one of C**H_3**), 1.24 (s, 3H, one of C**H_3**), 1.16 (ddd, *J* = 13.3, 8.0, 5.6 Hz, 1H), 1.07 (m, 18H, –SiCH(C**H_3**)$_2$), 1.07 (m, 3H, –SiC**H**$(CH_3)_2$), 1.04 (ddd, *J* = 13.3, 6.3, 2.2 Hz, 1H), 0.99–0.97 (m, *J* = 6.9 Hz, 6H, two of –CH(C**H_3**)), 0.96 (t, *J* = 8.0 Hz, 9H, –$SiCH_2C$**H_3**), 0.92–0.81 (m, 12H, four of –CH(C**H_3**)), 0.88 (s, 9H, one of C(C**H_3**)$_3$), 0.88 (t, *J* = 7.1 Hz, 3H, C_{48}-**H_3**), 0.86 (s, 9H, one of C(C**H_3**)$_3$), 0.84 (s, 9H, one of C(C**H_3**)$_3$), 0.83 (t, *J* = 7.9 Hz, 9H, –$SiCH_2C$**H_3**), 0.73 (d, *J* = 6.9 Hz, 3H, one of –CH(C**H_3**)), 0.70–0.58 (m, *J* = 7.9, 7.8 Hz, 6H, –SiC**H_2**CH_3), 0.43 (q, *J* = 8.0 Hz, 6H, –SiC**H_2**CH_3), 0.07 (s, 3H, one of SiC**H_3**), 0.03 (s, 3H, one of SiC**H_3**), 0.03 (s, 3H, one of SiC**H_3**), 0.01 (s, 3H, one of SiC**H_3**), –0.03 (s, 3H, one of SiC**H_3**), –0.13 (s, 3H, one of SiC**H_3**); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.8, 139.8, 138.8, 138.8, 137.9, 137.7, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.8, 127.4, 127.4, 127.4, 127.3, 127.3, 127.0, 107.5, 98.3, 98.3, 97.2, 80.9, 79.6, 78.9, 78.5, 77.2, 75.9, 75.9, 75.8, 75.5, 75.0, 74.8, 74.0, 73.6, 73.3, 73.0, 72.8, 72.8, 72.5, 71.5, 71.5, 71.0, 69.9, 69.7, 68.2, 67.3, 67.2, 48.7, 45.1, 42.5, 40.8, 40.7, 39.2, 39.1, 38.6, 37.9, 32.7, 32.4, 31.9, 31.9, 31.3, 30.6, 30.4, 30.1, 30.0, 29.8, 29.6, 29.6, 29.3, 28.6, 27.1, 27.0, 26.0, 26.0, 25.9, 25.8, 25.2, 22.7, 20.7, 20.1, 19.8, 19.3, 18.2, 18.2, 18.2, 18.0, 18.0, 14.1, 12.7, 11.0, 9.5, 9.0, 8.9, 6.9, 6.8, 5.1, 4.6, 4.5, –3.7, –3.8, –4.2, –4.4, –4.5, –4.7; HRMS (ESI-TOF) *m/z* calcd for $C_{139}H_{242}NaO_{22}Si_6$ $[M+Na]^+$: 2454.6326, found: 2454.6361.



(5*R*,8*S*,9*S*)-9-((4*R*,5*R*)-5-((2*S*,3*R*,4*S*,5*S*,6*S*,8*R*,10*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-11-((4*R*,5*S*,6*S*)-6-((*S*)-1-((4*S*,6*R*)-6-((*S*)-1-((4*R*,5*S*,6*S*)-6-((2*R*,3*R*,4*R*,6*R*,8*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3,9-dihydroxy-6,8-dimethylnonan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2,3,4,6,8-pentahydroxy-10-((triisopropylsilyl)oxy)undecyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-11,11-diethyl-2,2,3,3-tetramethyl-5-nonyl-8-((triethylsilyl)oxy)-4,10-dioxa-3,11-disilatridecan-7-one (56). To a solution of pentabenzyl ether **55** (0.11 g, 45 μmol, 1.0 equiv) in THF (0.30 mL, 0.15 M wrt **55**) and 6:1 dioxane/H_2O (0.15 mL, 0.30 M wrt **55**) at rt was added palladium black (~10 mg). The reaction mixture was purged with hydrogen for 1 min, stirred vigorously for 6 h, then recharged with additional catalyst at this time and approximately every 6 h thrice after (total palladium black added: ~50 mg). The reaction mixture was stirred at rt for 6 h, then filtered through Celite®. The filter cake was rinsed with THF (35 mL total), and the filtrate concentrated. Column chromatography (gradient elution, 1% → 1.5% EtOH in CH_2Cl_2) afforded heptaol **56** (84 mg, 93% yield) as a clear, colorless glass. $[\alpha]_D^{23}$ –5.1° (*c* = 2.1, CH_2Cl_2); IR (neat) 3448 (br), 2932, 2864, 1716, 1462, 1380, 1254, 1201, 1096, 1057, 1007, 981, 885, 837, 776, 743, 678 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.44 (m, 1H), 4.36 (m, *J* = 11.7, 4.9 Hz, 1H), 4.25 (m, *J* = 5.4, 4.4 Hz, 1H), 4.21 (m, *J* = 5.9, 5.4 Hz, 1H, C_{39}-**H**), 4.17–4.11 (m, 3H), 4.11–3.94 (m, 4H), 3.94–3.83 (m, 4H), 3.78–3.64 (m, 6H), 3.64–3.55 (m, 3H), 3.49 (dd, *J* = 10.5, 5.1 Hz, 1H), 3.42–3.37 (m, *J* = 9.8, 8.3 Hz, 2H, C_3-$\mathbf{H}_2$), 3.22 (m, *J* = 3.9 Hz, 1H), 2.92 (dd, *J* = 19.5, 5.4 Hz, 1H, one of C_{38}-**H**), 2.81 (dd, *J* = 19.5, 5.9 Hz, 1H, one of C_{38}-**H**), 2.08 (m, *J* = 9.8 Hz, 1H, C_3-O**H**), 1.93–1.81 (m, 6H), 1.79–

1.68 (m, 5H), 1.65 (m, J = 7.3, 7.3 Hz, 1H), 1.62–1.47 (m, 6H), 1.47 (s, 3H, one of C**H**$_3$), 1.45–1.22 (m, 16H, $C_{40–47}$-**H**$_2$), 1.43 (s, 3H, one of C**H**$_3$), 1.38 (s, 3H, one of C**H**$_3$), 1.36 (m, 1H), 1.36 (m, 1H, one of C_5-**H**), 1.36 (s, 3H, one of C**H**$_3$), 1.34 (s, 3H, one of C**H**$_3$), 1.34 (s, 3H, one of C**H**$_3$), 1.27 (s, 3H, one of C**H**$_3$), 1.25 (s, 3H, one of C**H**$_3$), 1.07 (m, 21H, –SiCH(C**H**$_3$)$_2$, and –SiC**H**(CH$_3$)$_2$), 1.03 (d, J = 6.8 Hz, 3H, one of –CH(C**H**$_3$)), 0.98 (m, 1H, one of C_5-**H**), 0.95 (t, J = 7.8 Hz, 18H, –SiCH$_2$C**H**$_3$), 0.95 (d, J = 7.8 Hz, 3H, one of –CH(C**H**$_3$)), 0.92 (d, J = 6.3 Hz, 3H, one of –CH(C**H**$_3$)), 0.92 (d, J = 6.3 Hz, 3H, one of –CH(C**H**$_3$)), 0.89 (s, 18H, two of C(C**H**$_3$)$_3$), 0.87 (t, 3H, C_{48}-**H**$_3$), 0.86 (d, 3H, one of –CH(C**H**$_3$)), 0.86 (s, 9H, one of C(C**H**$_3$)$_3$), 0.80 (d, J = 6.8 Hz, 3H, one of –CH(C**H**$_3$)), 0.67 (d, J = 5.9 Hz, 3H, one of –CH(C**H**$_3$)), 0.70–0.58 (m, J = 7.8, 7.3 Hz, 12H, –SiC**H**$_2$CH$_3$), 0.11 (s, 9H, three of SiC**H**$_3$), 0.10 (s, 3H, one of SiC**H**$_3$), 0.06 (s, 3H, one of SiC**H**$_3$), 0.02 (s, 3H, one of SiC**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 212.0, 108.1, 98.4, 98.2, 97.1, 79.1, 78.4, 75.8, 75.8, 75.0, 74.8, 74.7, 74.5, 73.5, 73.4, 73.3, 72.4, 71.3, 70.8, 70.5, 69.9, 69.5, 68.5, 68.2, 68.2, 67.2, 48.4, 43.9, 41.9, 41.9, 41.2, 40.0, 39.9, 39.2, 38.5, 37.8, 36.3, 33.3, 33.1, 32.9, 31.9, 31.8, 30.3, 30.0, 29.8, 29.7, 29.6, 29.5, 29.3, 28.4, 26.8, 25.9, 25.8, 25.8, 25.8, 25.1, 22.6, 20.8, 20.1, 19.7, 19.2, 18.1, 18.0, 18.0, 18.0, 17.1, 14.1, 12.7, 10.9, 9.3, 9.2, 9.1, 6.8, 6.8, 5.1, 4.7, 4.7, –3.4, –4.2, –4.4, –4.6, –4.6, –4.7; HRMS (ESI-TOF) m/z calcd for $C_{104}H_{213}O_{22}Si_6$ $[M+H]^+$: 1982.41586, found: 1982.41308.

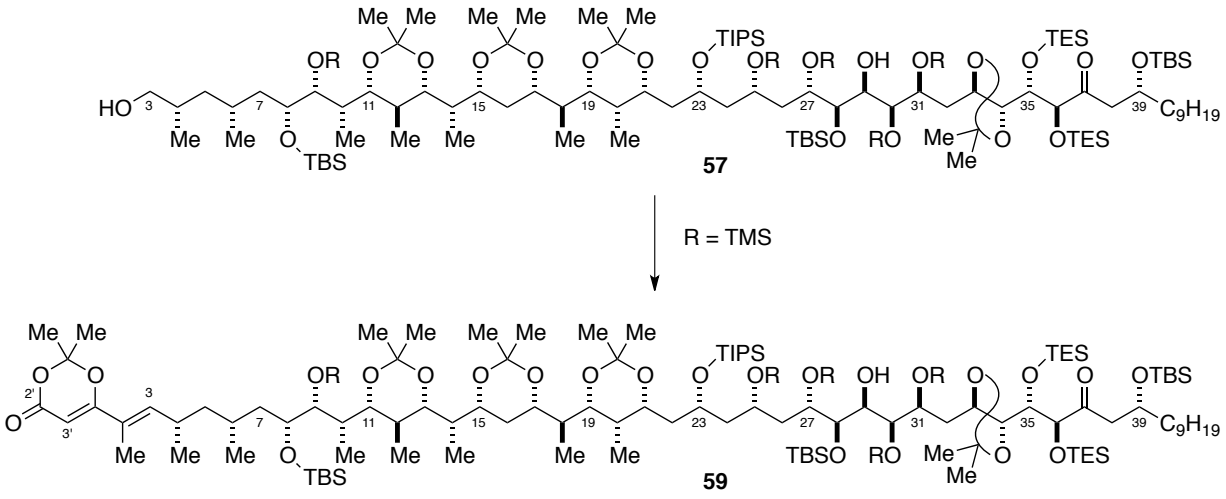


Primary carbinols 57. To a solution of heptaol **56** (0.10 g, 51 μmol, 1.0 equiv) and pyridine (58 μL, 0.72 mmol, 14 equiv) in CH_2Cl_2 (0.86 mL, 60 mM wrt **56**) at 0 °C was added chlorotrimethylsilane (65 μL, 0.51 mmol, 10 equiv). The reaction mixture was stirred at 0 °C

for 2 h, slowly warmed to rt over 2 h, stirred at rt for 2 d, quenched at 0 °C with H_2O (1 mL), and diluted with Et_2O (3 mL). The layers were separated and the aqueous layer extracted with 9:1 hexanes/EtOAc (5 x 2 mL). The combined organic extracts were filtered through a silica gel plug (4 cm), and the filter cake rinsed with 9:1 hexanes/EtOAc (50 mL). The filtrate was concentrated, then azeotroped with PhH (3 x 5 mL) to afford a crude mixture of regioisomeric hexakistrimethylsilyl ethers **164** as a clear, colorless oil that was used without further purification.

To a solution of crude trimethylsilyl ethers **164** (theoretical 0.13 g, 51 μmol, 1.0 equiv) in 4:1 CH_2Cl_2/iPrOH (1.3 mL, 0.04 M wrt **164**) at 0 °C was added PPTS (0.13 mg, 0.51 μmol, 0.01 equiv). The reaction mixture was stirred at 0 °C for 2 h, quenched with Et_3N (0.1 mL), stirred while warming to rt over 5 min, and filtered through a silica gel plug (4 cm). The filter cake was rinsed with 9:1 hexanes/EtOAc (50 mL), and the filtrate concentrated. Column chromatography (gradient elution, 3% → 3.5% → 4% EtOAc in hexanes) afforded a mixture of primary carbinols **57** (0.10 g, 87% yield, two steps) as a white foam. $[\alpha]_D^{23}$ –7.8° (*c* = 2.6, CH_2Cl_2); IR (neat) 3509 (br), 2955, 1718, 1463, 1379, 1252, 1201, 1094, 1056, 978, 840, 775, 746, 679 cm^{-1}; *partial list of resonances:* ^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.23–4.15 (m, *J* = 11.2, 2.9 Hz, 2H), 4.21 (m, *J* = 5.9, 5.8, 5.3 Hz, 1H, C_{39}-**H**), 4.18–4.15 (m, *J* = 11.2, 2.9 Hz, 2H), 3.89 (m, 1H), 3.84–3.76 (m, 3H), 3.75–3.65 (m, 4H), 3.63 (dd, *J* = 4.7, 3.5 Hz, 1H), 3.58–3.48 (m, 7H), 3.34 (ddd, *J* = 10.6, 7.0, 4.1 Hz, 1H), 2.91–2.83 (m, *J* = 6.5, 5.3 Hz, 2H, C_{38}-**H$_2$**), 2.70 (d, *J* = 8.3 Hz, 1H, CH-O**H**), 2.17–2.15 (m, 1H), 1.43 (s, 3H, one of C**H**$_3$), 1.41 (s, 3H, one of C**H**$_3$), 1.38 (s, 3H, one of C**H**$_3$), 1.37 (s, 3H, one of C**H**$_3$), 1.35 (s, 3H, one of C**H**$_3$), 1.34 (s, 3H, one of C**H**$_3$), 1.28 (s, 3H, one of C**H**$_3$), 1.21 (s, 3H, one of C**H**$_3$), 1.06 (m, 21H, –SiCH(C**H**$_3$)$_2$, 0.962 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H$_3$**), 0.958 (t, *J* = 7.9 Hz, 9H, –SiCH$_2$C**H$_3$**), 0.91 (s, 9H, one of C(C**H**$_3$)$_3$), 0.89 (d, *J* = 7.0 Hz, 3H, one of –CH(C**H**$_3$)), 0.89 (s, 9H, one of C(C**H**$_3$)$_3$), 0.87 (d, *J* = 7.1 Hz, 3H, one of –CH(C**H**$_3$)), 0.87 (d, *J* = 7.0 Hz, 3H, one of –CH(C**H**$_3$)), 0.86 (d, 3H, one of –CH(C**H**$_3$)), 0.86 (s, 9H, one of C(C**H**$_3$)$_3$), 0.85 (d, *J* = 7.1 Hz, 3H, one of –CH(C**H**$_3$)), 0.78 (d, *J* = 7.0 Hz, 3H, one of –CH(C**H**$_3$)), 0.70 (d, *J* = 7.0 Hz, 3H, one of –CH(C**H**$_3$)), 0.70–0.58 (m, 12H, –SiC**H$_2$**CH$_3$), 0.15 (s, 9H, one of –Si(C**H**$_3$)$_3$), 0.14 (s, 9H, one of –Si(C**H**$_3$)$_3$), 0.11 (s, 9H, one of –Si(C**H**$_3$)$_3$), 0.10 (s, 9H, one of –Si(C**H**$_3$)$_3$), 0.08 (s, 9H, one of –Si(C**H**$_3$)$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.8, 106.9, 98.5, 98.2, 97.2, 78.4,

78.3, 77.6, 77.3, 77.0, 76.2, 76.0, 75.1, 73.5, 73.2, 73.1, 72.5, 71.5, 70.6, 70.4, 68.1 (3C), 67.4, 67.3, 66.8, 48.9, 46.0, 41.8 (2C), 40.2, 39.6, 39.3, 38.6, 37.9, 34.8, 33.0, 31.9, 31.83, 31.80, 30.4, 30.1, 30.0, 29.8, 29.63, 29.59, 29.3, 28.8, 27.1, 26.1, 26.0, 25.9, 25.8, 25.2, 22.7, 20.9, 20.2, 20.0, 19.4, 18.4, 18.34, 18.30, 18.1, 18.0, 17.7, 14.1, 12.9, 11.1, 9.5, 8.9, 6.9, 5.2, 4.7, 1.35, 1.34, 0.95, 0.91, 0.78, –3.5 (2C), –4.0, –4.6, –4.7, –4.8; HRMS (ESI-TOF) *m/z* calcd for $C_{119}H_{252}NaO_{22}Si_{11}$ $[M+Na]^+$: 2364.58752, found: 2364.59544.

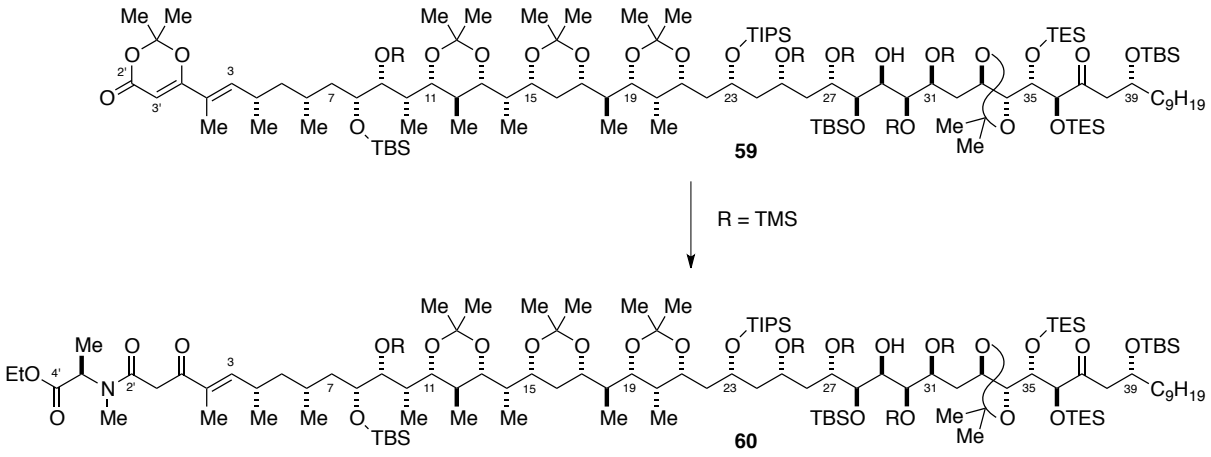


Dioxinones 59. To a solution of carbinols **57** (73 mg, 30 μmol, 1.0 equiv) and $EtN(iPr)_2$ (16 μL, 91 μmol, 3.0 equiv) in CH_2Cl_2 (0.43 mL, 0.07 M wrt **57**) and DMSO (0.10 mL, 0.3 M wrt **57**) at –30 °C was added a solution of SO_3•py (14 mg, 91 μmol, 3.0 equiv) in DMSO (0.30 mL, 0.3 M wrt SO_3•py). The reaction mixture was stirred between –30 °C and –20 °C for 1.5 h, charged with an additional solution of SO_3•py (14 mg, 91 μmol, 3.0 equiv) in DMSO (0.10 mL, 0.9 M wrt SO_3•py), stirred for an additional 3 h, quenched with brine (8 mL), then diluted with Et_2O (40 mL) and H_2O (1 mL). The layers were separated and the organic layer washed sequentially with 1 M aq $NaHSO_4$ (8 mL), sat. aq $NaHCO_3$ (8 mL), and 1:1 H_2O/brine (2 x 8 mL). The organic layer was then dried over Na_2SO_4 with added hexanes, filtered and concentrated. Benzene was added during concentration to prevent decomposition. Column chromatography (gradient elution, 2% → 3% EtOAc in hexanes) afforded a mixture of aldehydes **58** as a clear, colorless oil that was slightly wet with benzene.

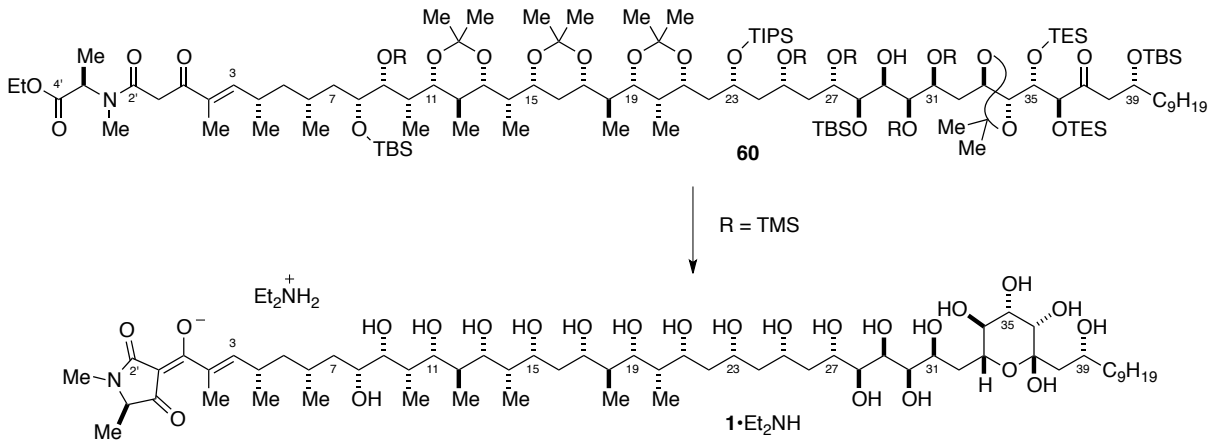
To a solution of dioxinone phosphonate **11** (27 mg, 91 μmol, 3.0 equiv) in THF (0.45 mL, 0.2 M wrt **11**) at –78 °C was added a freshly prepared solution of LDA in THF (0.18 mL, 0.5 M,

91 μmol, 3.0 equiv). The reaction mixture was slowly warmed to 0 °C over 1.5 h, stirred at 0 °C for 30 min, then recooled to –78 °C and charged with HMPA (0.10 mL, 0.3 M wrt **58**). The reaction mixture was stirred at –78 °C for 45 min, charged with a solution of aldehydes **58** (theoretical 73 mg, 30 μmol, 1.0 equiv) in THF (0.15 mL, 0.20 M wrt **58**), slowly warmed to 0 °C over 3 h, stirred at 0 °C for 3 h, quenched with brine (1 mL), then diluted with Et_2O (3 mL) and H_2O (0.2 mL). The biphasic mixture was directly filtered through a silica gel plug (4 cm), the filter cake rinsed with 9:1 hexanes/EtOAc (50 mL), and the filtrate concentrated. Column chromatography (gradient elution, 3% → 3.5% → 4% EtOAc in hexanes) afforded a mixture of dioxinones **59** (44 mg, 59% yield, two steps) as a white foam. $[\alpha]_D^{22}$ +2.5° (*c* = 2.2, CH_2Cl_2); IR (neat) 3506 (br), 2956, 2877, 1736, 1639, 1597, 1462, 1378, 1252, 1202, 1096, 1058, 1010, 978, 839, 776, 746, 678 cm^{-1}; *partial list of resonances:* ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.14 (d, *J* = 10.0 Hz, 1H, C_3-**H**), 5.40 (s, 1H, $C_{3'}$-**H**), 4.21–4.15 (m, 2H), 4.20 (m, *J* = 5.9, 5.8, 5.3 Hz, 1H, C_{39}-**H**), 4.12–4.06 (m, 2H), 3.92–3.87 (m, 1H), 3.86–3.75 (m, 3H), 3.69–3.65 (m, 4H), 3.59–3.44 (m, 7H), 2.91–2.83 (m, 2H, C_{38}-**H$_2$**), 2.70 (d, *J* = 8.2 Hz, 1H, CH-O**H**), 2.70–2.66 (m, 1H, C_4-**H**), 2.17–2.11 (m, 1H), 1.82 (s, 3H, C_2-C**H$_3$**), 1.70 (s, 6H, two of C**H**$_3$), 1.43 (s, 3H, one of C**H**$_3$), 1.41 (s, 3H, one of C**H**$_3$), 1.37 (s, 3H, one of C**H**$_3$), 1.36 (s, 3H, one of C**H**$_3$), 1.35 (s, 3H, one of C**H**$_3$), 1.33 (s, 3H, one of C**H**$_3$), 1.27 (s, 3H, one of C**H**$_3$), 1.21 (s, 3H, one of C**H**$_3$), 1.05 (m, 21H, –SiCH(C**H**$_3$)$_2$, 0.99 (d, *J* = 6.4 Hz, 3H, –C_4(C**H**$_3$)), 0.97 (d, 3H, one of –CH(C**H**$_3$)), 0.96 (t, *J* = 7.9 Hz, 18H, –$SiCH_2$C**H$_3$**), 0.90 (s, 9H, one of C(C**H**$_3$)$_3$), 0.87 (d, *J* = 7.1 Hz, 3H, one of –CH(C**H**$_3$)), 0.86 (s, 9H, one of C(C**H**$_3$)$_3$), 0.85 (s, 9H, one of C(C**H**$_3$)$_3$), 0.84 (d, *J* = 7.1 Hz, 3H, one of –CH(C**H**$_3$)), 0.82 (d, *J* = 7.1 Hz, 3H, one of –CH(C**H**$_3$)), 0.78 (d, *J* = 7.1 Hz, 3H, one of –CH(C**H**$_3$)), 0.69 (d, *J* = 6.4 Hz, 3H, one of –CH(C**H**$_3$)), 0.70–0.58 (m, 12H, –SiC**H$_2$**CH_3), 0.15 (s, 9H, one of –Si(C**H**$_3$)$_3$), 0.14 (s, 9H, one of –Si(C**H**$_3$)$_3$), 0.11 (s, 9H, one of –Si(C**H**$_3$)$_3$), 0.08 (s, 18H, two of –Si(C**H**$_3$)$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.9, 165.8, 162.4, 143.5, 125.7, 106.9, 105.9, 98.5, 98.2, 97.2, 91.4, 78.4, 78.3, 77.6, 77.5, 77.0, 76.8, 76.1, 76.0, 75.1, 73.5, 73.1, 73.0, 72.4, 71.5, 70.6, 70.4, 68.1, 67.4, 67.3, 66.8, 48.8, 46.0, 45.3, 40.7, 40.2, 39.6, 39.3, 38.6, 37.9, 36.6, 32.8, 31.9, 31.8, 31.7, 30.6, 30.4, 30.1, 30.0, 29.8, 29.63, 29.59, 29.3, 28.8, 28.4, 27.6, 26.9, 26.2, 26.1, 26.0, 25.9, 25.8, 25.7, 25.4, 25.2, 24.7, 24.6, 23.3, 22.7, 21.2, 20.3, 20.2, 20.0, 19.4, 18.4, 18.34, 18.30, 18.2, 18.02, 18.00, 14.1, 12.9, 12.3, 11.1, 9.5, 8.9, 8.8, 6.9, 5.2, 4.7, 1.39, 1.35, 0.94,

0.76 (2C), –3.5 (2C), –4.1, –4.6, –4.7, –4.8; HRMS (ESI-TOF) *m/z* calcd for $C_{127}H_{264}NO_{24}Si_{11}$ $[M+NH_4]^+$: 2495.69248, found: 2495.68105.



β-Ketoamides 60. A mixture of dioxinones **59** (12 mg, 4.7 μmol, 1.0 equiv), aminium chloride **9**•HCl (13 mg, 75 μmol, 16 equiv), and 4 Å molecular sieves (25 mg, 1:1 mass ratio wrt **59** + **9**•HCl) was azeotroped with 1:1 CH_2Cl_2/PhH (3 x 1 mL) in a 0.5 dram vial. The reaction vessel was charged with PhMe (94 μL, 50 mM wrt **59**), sealed with Teflon tape and parafilm, then heated to 110 °C for 7 h. The reaction mixture was cooled to rt, diluted with 9:1 CH_2Cl_2/MeOH (0.5 mL), and filtered through a silica gel plug (4 cm). The filter cake was rinsed with 9:1 CH_2Cl_2/MeOH (30 mL), and the filtrate concentrated. Column chromatography (gradient elution, 0.5% → 0.75% → 1% EtOAc in hexanes) afforded a mixture of β-ketoamides **60** (8.5 mg, 69% yield) as a clear, colorless oil. These β-ketoamides **60** existed as a complex mixture of rotamers and tautomers. *partial list of resonances:* ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.57–6.28 (3 x d, *J* = 10.0 Hz, 1H, C_3-**H**), 2.95–2.84 (3 x s, 3H, N-C**H**$_3$), 2.91–2.83 (m, 2H, C_{38}-**H**$_2$), 2.75–2.68 (m, 1H, C_4-**H**), 2.70 (d, *J* = 8.2 Hz, 1H, CH-O**H**), 1.82 (s, 3H, C_2-C**H**$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.9, 195.1, 171.7, 168.0, 150.8, 135.2, 106.9, 98.5, 98.2, 97.2.



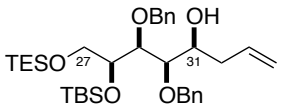
Aflastatin A diethylamine salt (1•Et_2NH). To a solution of β-ketoamides **60** (19 mg, 7.4 μmol, 1.0 equiv) in 1:1 THF/TMSOH (0.37 mL, 0.02 M wrt **60**) at 0 °C was added KOTMS (2.3 mg, 16 μmol, 2.2 equiv). The reaction mixture was stirred at 0 °C for 2.5 h, charged with additional KOTMS (9.5 mg, 74 μmol, 10 equiv), then stirred for an additional 45 min. The reaction mixture was quenched at 0 °C with AcOH (8 μL, 15 μmol, 20 equiv), warmed to rt and stirred for 30 min, diluted with 19:1 CH_2Cl_2/CH_3OH (1 mL), and filtered through a silica gel plug (4 cm). The filter cake was rinsed with 19:1 CH_2Cl_2/CH_3OH (30 mL), and the filtrate concentrated to afford a mixture of tetramic acids **61** as a pale reddish orange solid.

To a solution of tetramic acids **61** (theoretical 19 mg, 7.4 μmol, 1.0 equiv) in 3:2 CH_2Cl_2/ CH_3CN (0.5 mL, 15 mM wrt **61**) at 0 °C was added dropwise a solution of fluorosilicic acid (H_2SiF_6) in H_2O (~60 μL, 20–25 wt. %). The reaction mixture was diluted with CH_3CN (0.4 mL), then immediately warmed to rt and stirred for 1 d. The reaction mixture was quenched with TMSOMe (0.5 mL), stirred for 15 min, then filtered through Celite®, and the filter cake rinsed with 4:1 CH_2Cl_2/CH_3OH (100 mL total). The filtrate was concentrated, triturated with THF (5 x 0.3 mL), and azeotroped with 1% Et_2NH in CH_3OH (3 x 5 mL). Purification by reversed-phase HPLC (gradient elution, 65% → 80% CH_3OH in H_2O + 0.5% Et_2NH, 20 min runtime) on a C18 column (Capcell Pak C18 UG, 5 μm, 120 Å, 250 mm x 10 mm) and lyophilization afforded the diethylamine salt of aflastatin A (**1**•Et_2NH) (3.6 mg, 36% yield, two steps) as a white solid. $[\alpha]_D^{26}$ –2.80° (*c* = 0.55, DMSO); IR (neat) 3321 (br), 2924, 2853, 1600, 1450, 1379, 1314, 1209, 1154, 1065, 968, 843 cm^{-1}; ^{1}H-NMR (600 MHz, DMSO-d_6) δ 6.13 (br s, 1H, C_{37}-O**H**), 5.42 (d, *J* = 9.9 Hz, 1H, C_3-**H**), 5.28 (br s, 1H, C_{25}-O**H**), 5.27 (br s,

1H, C_{13}-O**H**), 5.19 (br s, 1H, C_{11}-O**H**), 5.02 (br s, 1H, C_8-O**H**), 4.85 (br s, 1H, C_{39}-O**H**), 4.80 (br s, 1H, C_{15}-O**H**), 4.79 (br s, 1H, C_{23}-O**H**), 4.75 (br s, 1H, C_{21}-O**H**), 4.72 (br s, 1H, C_{17}-O**H**), 4.71 (br s, 1H, C_{27}-O**H**), 4.64 (br s, 1H, C_{34}-O**H**), 4.62 (br s, 1H, C_{28}-O**H**), 4.60 (br s, 1H, C_{19}-O**H**), 4.49 (br s, 1H, C_{36}-O**H**), 4.42 (br s, 1H, C_9-O**H**), 4.40 (br s, 1H, C_{35}-O**H**), 4.17 (br s, 2H, C_{30}-O**H** and C_{31}-O**H**), 4.15 (br s, 1H, C_{29}-O**H**), 3.90 (m, 1H, C_{17}-**H**), 3.87 (m, 1H, C_{25}-**H**), 3.86 (m, 2H, C_{15}-**H** and C_{39}-**H**), 3.85 (m, 2H, C_{29}-**H** and C_{31}-**H**), 3.79 (m, 1H, C_{21}-**H**), 3.76 (m, 1H, C_{23}-**H**), 3.69 (m, *J* = 7.6 Hz, 1H, C_{13}-**H**), 3.68 (m, 1H, C_{11}-**H**), 3.64 (m, *J* = 7.6 Hz, 1H, C_8-**H**), 3.62 (m, *J* = 7.0 Hz, 2H, C_{27}-**H** and C_{33}-**H**), 3.56 (m, *J* = 7.1 Hz, 1H, C_{35}-**H**), 3.44 (m, 2H, C_{19}-**H** and C_{30}-**H**), 3.39 (m, 1H, C_{36}-**H**), 3.26 (m, 2H, C_9-**H** and C_{28}-**H**), 3.24 (q, *J* = 6.4 Hz, 1H, $C_{5'}$-**H**), 3.17 (dd, *J* = 9.4, 9.4 Hz, 1H, C_{34}-**H**), 2.70 (s, 3H, $C_{7'}$-$\mathbf{H_3}$), 2.53 (m, 1H, C_4-**H**), 2.05 (m, *J* = 10.6, 7.1 Hz, 1H, one of C_{32}-**H**), 1.88 (m, 1H, C_6-**H**), 1.83 (m, 1H, one of C_{26}-**H**), 1.82 (m, *J* = 12.9 Hz, 1H, one of C_{38}-**H**), 1.81 (m, 1H, C_{10}-**H**), 1.69 (s, 3H, C_{49}-$\mathbf{H_3}$), 1.66 (m, 1H, C_{14}-**H**), 1.65 (m, 1H, C_{18}-**H**), 1.61 (m, *J* = 8.2, 7.6 Hz, 2H, C_{12}-**H**, and one of C_{16}-**H**), 1.56 (m, 1H, one of C_{24}-**H**), 1.55–1.50 (m, 3H, C_{20}-**H** and C_{22}-$\mathbf{H_2}$), 1.46 (m, 1H, one of C_{32}-**H**), 1.41 (dd, *J* = 14.1, 10.5 Hz, 1H, one of C_{38}-**H**), 1.40 (m, 1H, one of C_{24}-**H**), 1.33 (m, 2H, one of C_5-**H**, and one of C_{26}-**H**), 1.30 (m, 3H, one of C_{16}-**H**, and C_{40}-$\mathbf{H_2}$), 1.28–1.18 (m, 14H, $C_{41–47}$-$\mathbf{H_2}$), 1.25 (m, 2H, C_7-$\mathbf{H_2}$), 1.12 (d, *J* = 7.0 Hz, 3H, $C_{6'}$-$\mathbf{H_3}$), 0.94 (m, 1H, one of C_5-**H**), 0.88 (d, *J* = 6.4 Hz, 3H, C_{50}-$\mathbf{H_3}$), 0.85–0.83 (m, 9H, C_{48}-$\mathbf{H_3}$, C_{52}-$\mathbf{H_3}$, and C_{51}-$\mathbf{H_3}$), 0.81 (d, *J* = 6.5 Hz, 3H, C_{54}-$\mathbf{H_3}$), 0.78 (d, *J* = 6.4 Hz, 3H, C_{56}-$\mathbf{H_3}$), 0.68 (d, *J* = 7.0 Hz, 3H, C_{55}-$\mathbf{H_3}$), 0.64 (d, *J* = 6.5 Hz, 3H, C_{53}-$\mathbf{H_3}$); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 193.3 (C4'), 191.8 (C1), 173.5 (C2'), 138.8 (C3), 135.0 (C2), 98.4 (C37), 98.2 (C3'), 79.0 (C13), 76.2 (C19), 75.8 (C11), 74.9 (C9), 74.5 (C15), 74.3 (C28), 73.5 (C21), 73.0 (C36), 72.4 (C30), 71.2 (C34), 70.7 (C35), 70.2 (C17), 70.1 (C33), 69.7 (C27), 69.3 (C29), 68.6 (2C, C25 and C31), 67.9 (C23), 67.5 (C39), 67.2 (C8), 59.4 (C5'), 44.7 (C5), 44.5 (C24), 42.7 (C7), 41.8 (C18, C22 or C38), 41.7 (C18, C22 or C38), 41.6 (C18, C22 or C38), 41.0 (C26), 38.25 (C12, C14, C20 or C40), 38.21 (C12, C14, C20 or C40), 38.1 (C12, C14, C20 or C40), 38.0 (C12, C14, C20 or C40), 37.1 (C10), 35.8 (C32), 34.8 (C16), 31.3 (C46), 29.8 (C4), 29.2 (C42), 29.1 (C43 or C44), 29.0 (C43 or C44), 28.7 (C45), 26.3 (C7'), 26.2 (C6), 24.9 (C41), 22.1 (C47), 21.4 (C50), 20.7 (C51), 15.9 (C6'), 14.0 (C48), 13.4 (C49), 12.8 (C53), 10.5 (C55), 8.7 (C52), 6.4 (C54), 5.8 (C56); HRMS (ESI-TOF) *m/z* calcd for $C_{62}H_{115}NNaO_{24}$ $[M+Na]^+$: 1280.77012, found: 1280.77464.

Stereochemical Proof by Mosher's Ester Analysis

Homoallylic alcohol 46



46

H	δ_S (ppm)	δ_R (ppm)	$\Delta\delta = \delta_S - \delta_R$	
C_{27}-H_2	3.73	3.70	+0.03	L_2
	3.53	3.52	+0.01	
C_{28}-H	4.02	3.96	+0.06	
C_{29}-H	3.63	3.60	+0.03	
C_{30}-H	3.91	3.91	0.00	
$PhCH_2O$	4.71	4.65	+0.06	
	4.61	4.49	+0.12	
$PhCH_2O$	4.66	4.56	+0.10	
	4.61	4.56	+0.05	
TBS	0.90	0.90	0.00	
	0.09	0.09	0.00	
	0.08	0.08	0.00	
TES	0.87	0.88	–0.01	
	0.48	0.50	–0.02	
C_{32}-H	2.42	2.47	–0.05	L_3
	2.22	2.31	–0.09	
C_{33}-H	5.59	5.68	–0.09	
C_{34}-H	4.96	5.03	–0.07	
	4.90	4.98	–0.08	

Appendix

1

Spectral Data Comparisons

General Key to Tables

[a] Spectra of naturally derived aflastatin A (AsA) C3–C48 degradation polyol ("**1a**") were acquired in pyridine-d_5 at 150 MHz (^{13}C-NMR) or 600 MHz (^{1}H-NMR): H. Ikeda, N. Matsumori, M. Ono, A. Suzuki, A. Isogai, H. Nagasawa, S. Sakuda, *J. Org. Chem.* **2000**, *65*, 438–444.

[b] Spectra of synthetic aflastatin A (AsA) C3–C48 degradation polyol (**1a**), AsA C3–C48 degradation lactol methyl ethers **1b** and **1c**, model C27–C48 lactols **2a/2d–2h**, and model C27–C48 lactol methyl ethers **2b** and **2c** were acquired in pyridine-d_5 at 125 MHz (^{13}C-NMR) or 600 MHz (^{1}H-NMR).

[c] These values were corrected from those reported in 2000: S. Sakuda, N. Matsumori, K. Furihata, H. Nagasawa, *Tetrahedron Lett.* **2007**, *48*, 2527–2531.

[e] Spectra of naturally derived blasticidin A (BcA) C3–C47 degradation polyol (**3a**) were acquired in pyridine-d_5 at 125 MHz (^{13}C-NMR) or 500 MHz (^{1}H-NMR): S. Sakuda, H. Ikeda, T. Nakamura, R. Kawachi, T. Kondo, M. Ono, M. Sakurada, H. Inagaki, R. Ito, H. Nagasawa, *J. Antibiotics* **2000**, *53*, 1378–1384.

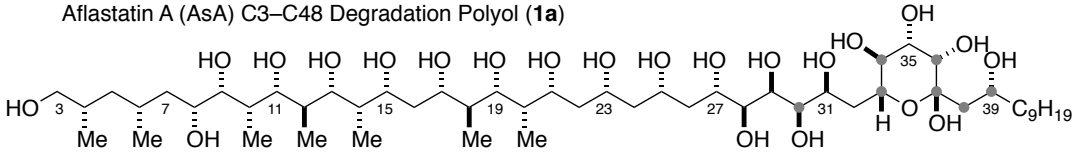
Atoms for BcA degradation polyol **3a** and BcA degradation lactol methyl ether **3b** have been renumbered so that they correlate to AsA polyol **2**. Only data for the structurally homologous lactol region is shown.

[g] Spectra of naturally derived aflastatin A (AsA) diethylamine salt (**4**•Et_2NH) were acquired in DMSO-d_6 at 125 MHz (^{13}C-NMR) or 500 MHz (^{1}H-NMR): (a) Sakuda, S.; Ono, M.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Am. Chem. Soc.* **1996**, *118*, 7855–7856; (b) Ono, M.; Sakuda, S.; Ikeda, H.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Antibiotics* **1998**, *51*, 1019–1028.

[h] Spectra of synthetic aflastatin A (AsA) diethylamine salt (**4**•Et_2NH) were acquired in DMSO-d_6 at 125 MHz (^{13}C-NMR) or 600 MHz (^{1}H-NMR).

Table 1. Contrast Between ^{13}C-NMR Data for Naturally Derived and Synthetic Aflastatin A (AsA) C3–C48 Degradation Polyols **1a**.[d]

Aflastatin A (AsA) C3–C48 Degradation Polyol (**1a**)



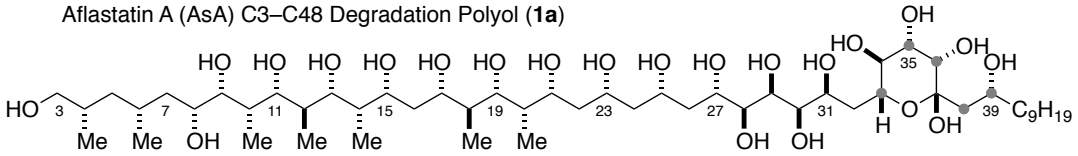
$|\Delta\delta| \geq \pm 1$ ppm

AsA #	Natural "1a"[a]	Synthetic 1a[b]	AsA #	Natural "1a"[a]	Synthetic 1a[b]
3	67.2	67.3	**28**	76.2[c]	76.1
			29	71.5	71.4
4	34.0	34.0	**30**	75.4	74.2
5	41.6	41.6	**31**	70.9	71.0
			32	37.5	37.4
6	27.8	27.9			
7	42.3	42.4	**33**	72.8	71.7
			34	72.3	73.3
8	69.5	69.5	**35**	72.6	72.9
9	77.9	78.0	**36**	71.5	75.1
10	38.1	38.1	**37**	103.2	100.1
11	78.8	78.9	**38**	39.3	42.8
12	38.8	38.8			
13	81.6	81.6	**39**	66.9	69.0
14	39.3	39.5	**40**	39.3	39.6
15	77.1	77.1			
16	45.7	45.7	**41**	26.0	25.9
17	73.9	74.0	**42**	29.8	29.8
18	42.7	42.7	**43**	30.0	29.9
19	78.8	78.8	**44**	30.0	30.1
20	39.5	39.5	**45**	29.5	29.6
21	76.2	76.3	**46**	32.0	32.1
22	42.7	42.7	**47**	22.9	22.9
			48	14.2	14.3
23	70.8	70.7	**49**	18.6	18.7
24	36.9	37.0	**50**	21.7	21.7
			51	8.3	8.3
25	71.1[c]	71.3	**52**	13.2	13.2
26	42.1	42.1	**53**	6.4	6.4
			54	11.6	11.7
27	72.2[c]	72.3	**55**	6.1	6.1

[d] Tabulated values in grey are $|\Delta\delta| \geq \pm 1$ ppm.

Table 2. Contrast Between [1]H-NMR Data for Naturally Derived and Synthetic Aflastatin A (AsA) C3–C48 Degradation Polyols **1a**.[d]

Aflastatin A (AsA) C3–C48 Degradation Polyol (**1a**)



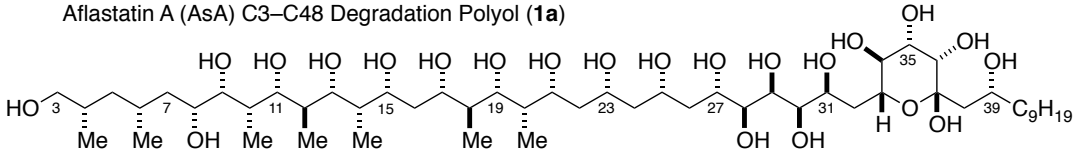
$|\Delta\delta| \geq \pm 0.1$ ppm

AsA #	Natural "1a"[a]	Synthetic 1a[b]	AsA #	Natural "1a"[a]	Synthetic 1a[b]
3	3.80	3.80	**28**	4.34[c]	4.30
	3.61	3.61	**29**	4.96	5.03
4	1.98	1.99	**30**	4.49	4.58
5	1.78	1.77	**31**	4.92	4.97
	1.04	1.05	**32**	3.17	3.21
6	2.14	2.15		2.49	2.56
7	1.84	1.83	**33**	4.24	4.85
	1.75	1.74	**34**	4.32	4.38
8	4.29	4.29	**35**	4.56	4.76
9	4.00	4.00	**36**	4.64	4.48
10	2.31	2.31	**37**		
11	4.32	4.32	**38**	2.45	2.14
12	2.08	2.08		2.19	2.73
13	4.12	4.12	**39**	4.18	4.72
14	1.97	1.95	**40**	1.67	1.65
15	4.49	4.48		1.59	1.51
16	2.04	2.04	**41**	1.59	1.51
	1.95	1.96		1.48	1.35
17	4.61	4.61	**42**	1.25	1.16
18	2.19	2.21	**43**	1.19	1.16
19	4.05	4.06	**44**	1.19	1.16
20	1.86	1.87	**45**	1.19	1.16
21	4.42	4.43	**46**	1.19	1.16
22	2.04	2.04	**47**	1.23	1.22
	1.86	1.86	**48**	0.83	0.83
23	4.49	4.48	**49**	1.10	1.10
24	2.05	2.03	**50**	1.07	1.06
	1.98	2.03	**51**	1.28	1.27
25	4.67	4.62	**52**	0.81	0.80
26	2.59	2.60	**53**	1.23	1.24
	2.14	2.16	**54**	0.97	0.97
27	4.67[c]	4.68	**55**	1.19	1.20

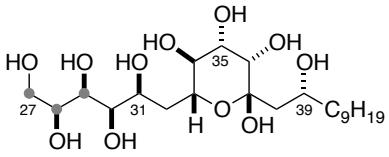
[d] Tabulated values in grey are $|\Delta\delta| \geq \pm 0.1$ ppm.

Table 3. Contrast Between NMR Data for Naturally Derived and Synthetic Aflastatin A (AsA) C3–C48 Degradation Polyols **1a**, and Model C27–C48 Lactol **2a**.[d]

Aflastatin A (AsA) C3–C48 Degradation Polyol (**1a**)



C27–C48 Model Lactol **2a**



^{13}C-NMR: $|\Delta\delta| \geq \pm 1$ ppm

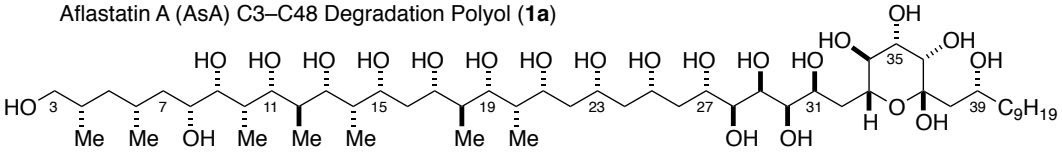
^{1}H-NMR: $|\Delta\delta| \geq \pm 0.1$ ppm

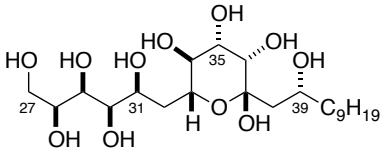
	^{13}C-NMR			^{1}H-NMR		
AsA #	**Natural "1a"**[a]	**Synthetic 1a**[b]	**Model 2a**[b]	**Natural "1a"**[a]	**Synthetic 1a**[b]	**Model 2a**[b]
27	72.2[c]	72.3	64.6	4.67[c]	4.68	4.33
28	76.2[c]	76.1	72.9	4.34[c]	4.30	4.61
29	71.5	71.4	73.5	4.96	5.03	4.72
30	75.4	74.2	73.7	4.49	4.58	4.61
31	70.9	71.0	71.6	4.92	4.97	5.00
32	37.5	37.4	37.5	3.17	3.21	3.22
				2.49	2.56	2.58
33	72.8	71.7	71.6	4.24	4.85	4.89
34	72.3	73.3	73.8	4.32	4.38	4.41
35	72.6	72.9	72.9	4.56	4.76	4.79
36	71.5	75.1	75.2	4.64	4.48	4.50
37	103.2	100.1	100.2			
38	39.3	42.8	42.6	2.45	2.14	2.15
				2.19	2.73	2.75
39	66.9	69.0	69.0	4.18	4.72	4.76
40	39.3	39.6	39.6	1.67	1.65	1.64
				1.59	1.51	1.53
41	26.0	25.9	25.8	1.59	1.51	1.51
				1.48	1.35	1.36
42	29.8	29.8	29.8	1.25	1.16	1.14
43	30.0	29.9	29.9	1.19	1.16	1.14
44	30.0	30.1	30.1	1.19	1.16	1.14
45	29.5	29.6	29.6	1.19	1.16	1.14
46	32.0	32.1	32.1	1.19	1.16	1.14
47	22.9	22.9	22.9	1.23	1.22	1.21
48	14.2	14.3	14.3	0.83	0.83	0.83

[d] With respect to synthetic **1a**, tabulated values in grey are $|\Delta\delta| \geq \pm 1$ ppm (^{13}C-NMR) or $|\Delta\delta| \geq \pm 0.1$ ppm (^{1}H-NMR).

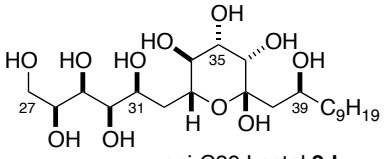
Table 4. Contrast Between ^{13}C-NMR Data for Naturally Derived Aflastatin A (AsA) C3–C48 Degradation Polyol **1a**, and Model C27–C48 Lactols **2a/2d–2h**.[d]

Aflastatin A (AsA) C3–C48 Degradation Polyol (**1a**)

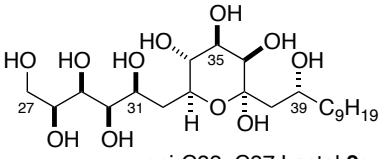




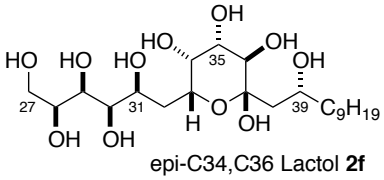
AsA Model Lactol **2a**



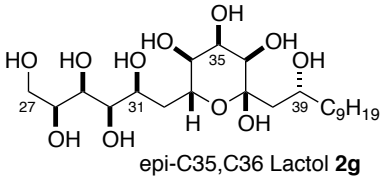
epi-C39 Lactol **2d**



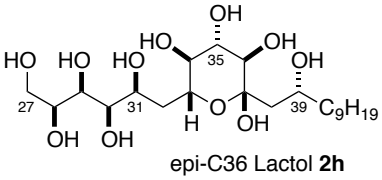
epi-C33–C37 Lactol **2e**



epi-C34,C36 Lactol **2f**



epi-C35,C36 Lactol **2g**



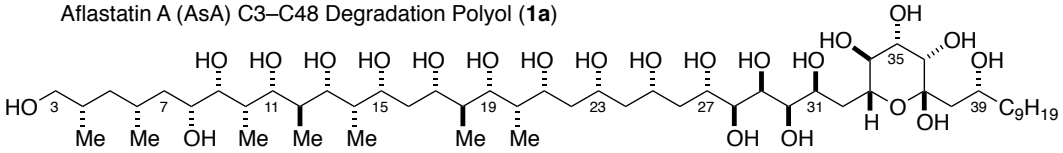
epi-C36 Lactol **2h**

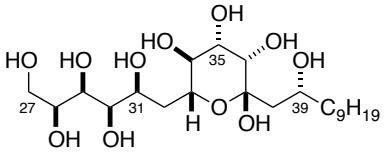
AsA #	Natural "1a"[a]	Model 2a[b]	Model 2d[b]	Model 2e[b]	Model 2f[b]	Model 2g[b]	Model 2h[b]
27	72.2[c]	64.6	64.6	64.6	64.5	64.6	64.5
28	76.2[c]	72.9	74.1	73.2	73.9	74.0	73.6
29	71.5	73.5	73.3	74.0	74.2	73.5	75.8
30	75.4	73.7	74.8	73.3	73.5	74.0	73.8
31	70.9	71.6	72.4	69.9	70.6	71.6	71.5
32	37.5	37.5	37.3	38.5	35.7	37.2	37.6
33	72.8	71.6	72.9	71.1	69.3	67.3	70.7
34	72.3	73.8	72.9	73.0	72.1	73.1	77.1
35	72.6	72.9	73.1	76.1	72.5	74.4	73.1
36	71.5	75.2	74.2	74.0	74.3	71.8	77.8
37	103.2	100.2	100.3	100.2	100.1	100.8	99.8
38	39.3	42.6	45.3	44.8	43.8	45.7	43.8
39	66.9	69.0	67.6	67.9	68.2	67.8	68.3
40	39.3	39.6	39.1	39.0	39.2	38.9	39.2
41	26.0	25.8	26.2	26.2	25.8	26.0	25.8
42	29.8	29.8	29.8	29.8	29.8	29.8	29.8
43	30.0	29.9	30.0	30.0	29.9	29.9	29.9
44	30.0	30.1	30.0	30.0	30.0	30.1	30.1
45	29.5	29.6	29.6	29.6	29.5	29.6	29.5
46	32.0	32.1	32.1	32.1	32.0	32.1	32.0
47	22.9	22.9	22.9	22.9	22.9	22.9	22.9
48	14.2	14.3	14.3	14.3	14.2	14.3	14.2

[d] With respect to naturally derived "**1a**", tabulated values in grey are $|\Delta\delta| \geq \pm 1$ ppm.

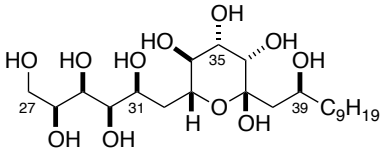
Table 5. Contrast Between ^{1}H-NMR Data for Naturally Derived Aflastatin A (AsA) C3–C48 Degradation Polyol **1a**, and Model C27–C48 Lactols **2a/2d–2h**.[d]

Aflastatin A (AsA) C3–C48 Degradation Polyol (**1a**)

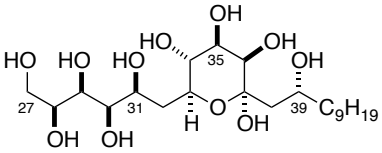




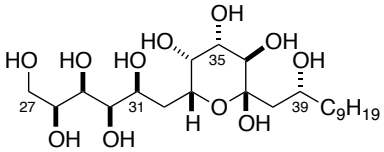
AsA Model Lactol **2a**



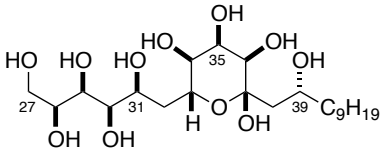
epi-C39 Lactol **2d**



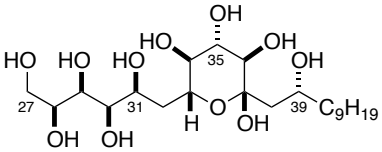
epi-C33–C37 Lactol **2e**



epi-C34,C36 Lactol **2f**



epi-C35,C36 Lactol **2g**

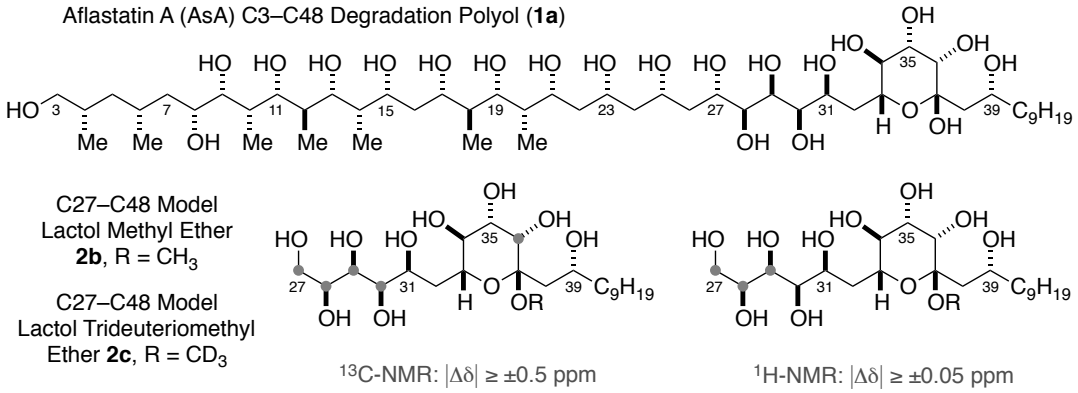


epi-C36 Lactol **2h**

AsA #	Natural "1a"[a]	Model 2a[b]	Model 2d[b]	Model 2e[b]	Model 2f[b]	Model 2g[b]	Model 2h[b]
27	4.67[c]	4.33	4.31	4.32	4.32	4.32	4.32
28	4.34[c]	4.61	4.54	4.55	4.59	4.59	4.58
29	4.96	4.72	4.56	4.64	4.48	4.67	4.70
30	4.49	4.61	4.43	4.91	4.68	4.52	4.58
31	4.92	5.00	4.83	4.90	4.85	4.92	4.95
32	3.17	3.22	3.07	3.11	2.96	3.09	3.21
	2.49	2.58	2.53	2.32	2.69	2.51	2.51
33	4.24	4.89	4.87	5.04	5.07	4.91	4.90
34	4.32	4.41	4.42	4.38	4.44	3.86	3.94
35	4.56	4.79	4.88	4.30	4.56	4.70	4.59
36	4.64	4.50	4.59	4.58	4.38	3.91	3.91
37							
38	2.45	2.15	2.48	2.38	2.64	2.45	2.67
	2.19	2.75	2.62	2.70	2.04	2.16	2.06
39	4.18	4.76	4.59	4.55	4.69	4.58	4.69
40	1.67	1.64	1.75	1.74	1.62	1.67	1.63
	1.59	1.53	1.60	1.60	1.48	1.54	1.50
41	1.59	1.51	1.60	1.60	1.48	1.54	1.50
	1.48	1.36	1.46	1.44	1.33	1.42	1.38
42	1.25	1.14	1.15	1.15	1.15	1.16	1.14
43	1.19	1.14	1.15	1.15	1.15	1.16	1.14
44	1.19	1.14	1.15	1.15	1.15	1.16	1.14
45	1.19	1.14	1.15	1.15	1.15	1.16	1.14
46	1.19	1.14	1.15	1.15	1.15	1.16	1.14
47	1.23	1.21	1.19	1.19	1.20	1.20	1.20
48	0.83	0.83	0.82	0.82	0.82	0.82	0.82

[d] With respect to naturally derived "**2**", tabulated values in grey are $|\Delta\delta| \geq \pm 0.1$ ppm.

Table 6. Contrast Between NMR Data for Naturally Derived Aflastatin A (AsA) C3–C48 Degradation Polyol **1a**, and Model C27–C48 Lactol Methyl Ethers **2b** and **2c**.[d]

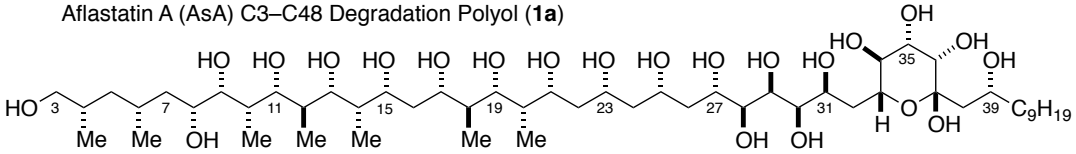


AsA #	^{13}C-NMR Natural "1a"[a]	^{13}C-NMR Model 2b[b]	^{13}C-NMR Model 2c[b]	^{1}H-NMR Natural "1a"[a]	^{1}H-NMR Model 2b[b]	^{1}H-NMR Model 2c[b]
27	72.2[c]	64.7	64.6	4.67[c]	4.35	4.35
28	76.2[c]	73.9	73.9	4.34[c]	4.65	4.65
29	71.5	73.6	73.6	4.96	4.68	4.68
30	75.4	74.3	74.3	4.49	4.52	4.52
31	70.9	71.3	71.3	4.92	4.94	4.94
32	37.5	37.5	37.5	3.17	3.20	3.20
				2.49	2.50	2.50
33	72.8	72.8	72.8	4.24	4.26	4.26
34	72.3	72.4	72.4	4.32	4.33	4.33
35	72.6	72.7	72.6	4.56	4.58	4.58
36	71.5	73.1	73.1	4.64	4.68	4.68
37	103.2	103.3	103.3			
38	39.3	39.4	39.4	2.45	2.46	2.46
				2.19	2.23	2.22
39	66.9	67.0	66.9	4.18	4.19	4.19
40	39.3	39.4	39.4	1.67	1.68	1.68
				1.59	1.60	1.60
41	26.0	26.0	26.0	1.59	1.60	1.58
				1.48	1.48	1.48
42	29.8	29.8	29.8	1.25	1.23	1.23
43	30.0	30.0	30.0	1.19	1.17	1.17
44	30.0	30.0	30.0	1.19	1.17	1.17
45	29.5	29.5	29.5	1.19	1.17	1.17
46	32.0	32.1	32.1	1.19	1.17	1.17
47	22.9	22.9	22.9	1.23	1.21	1.21
48	14.2	14.2	14.2	0.83	0.82	0.82
–OMe	n/a	47.9	n/a	n/a	3.37	n/a

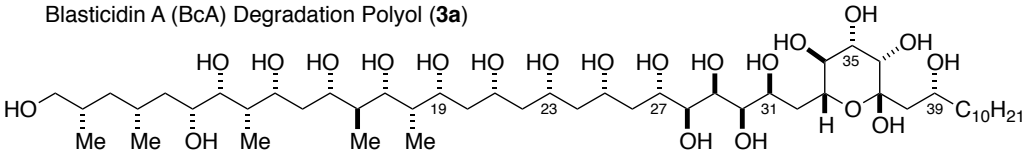
[d] With respect to naturally derived "**2**", tabulated values in grey are $|\Delta\delta| \geq \pm 0.5$ ppm (^{13}C-NMR) or $|\Delta\delta| \geq \pm 0.05$ ppm (^{1}H-NMR).

Table 7. Comparison of ^{13}C-NMR Data for Aflastatin A (AsA) C3–C48 Degradation Polyols **1a** and Blasticidin A (BcA) Degradation Polyol **3a**.[d]

Aflastatin A (AsA) C3–C48 Degradation Polyol (**1a**)



Blasticidin A (BcA) Degradation Polyol (**3a**)

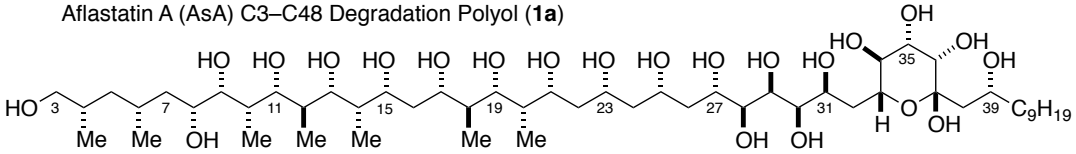


AsA #	Natural "1a"[a]	Natural 3a[f]	Synthetic 1a[b]	AsA #	Natural "1a"[a]	Natural 3a[f]	Synthetic 1a[b]
3	67.2		67.3	**28**	76.2[c]	76.1	76.1
				29	71.5	71.3	71.4
4	34.0		34.0	**30**	75.4	74.2	74.2
5	41.6		41.6	**31**	70.9	70.7	71.0
				32	37.5	37.5	37.4
6	27.8		27.9				
7	42.3		42.4	**33**	72.8	71.7	71.7
				34	72.3	73.4	73.3
8	69.5		69.5	**35**	72.6	72.9	72.9
9	77.9		78.0	**36**	71.5	75.1	75.1
10	38.1		38.1	**37**	103.2	100.1	100.1
11	78.8		78.9	**38**	39.3	42.9	42.8
12	38.8		38.8				
13	81.6		81.6	**39**	66.9	69.1	69.0
14	39.3		39.5	**40**	39.3	39.6	39.6
15	77.1		77.1				
16	45.7		45.7	**41**	26.0	25.9	25.9
17	73.9		74.0	**42**	29.8		29.8
18	42.7		42.7	**43**	30.0		29.9
19	78.8		78.8	**44**	30.0		30.1
20	39.5		39.5	**45**	29.5		29.6
21	76.2	70.8	76.3	**46**	32.0		32.1
22	42.7	45.7	42.7	**47**	22.9		22.9
				48	14.2		14.3
23	70.8	70.7	70.7	**49**	18.6		18.7
24	36.9	45.7	37.0	**50**	21.7		21.7
				51	8.3		8.3
25	71.1[c]	71.3	71.3	**52**	13.2		13.2
26	42.1	42.2	42.1	**53**	6.4		6.4
				54	11.6		11.7
27	72.2[c]	72.2	72.3	**55**	6.1		6.1

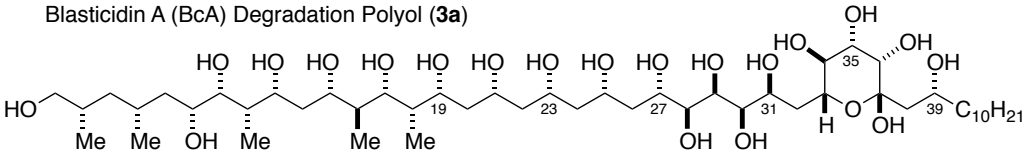
[d] Tabulated values in grey are $|\Delta\delta| \leq \pm 0.3$ ppm.

Table 8. Comparison of ^{1}H-NMR Data for Aflastatin A (AsA) C3–C48 Degradation Polyols **1a** and Blasticidin A (BcA) Degradation Polyol **3a**.[d]

Aflastatin A (AsA) C3–C48 Degradation Polyol (**1a**)



Blasticidin A (BcA) Degradation Polyol (**3a**)

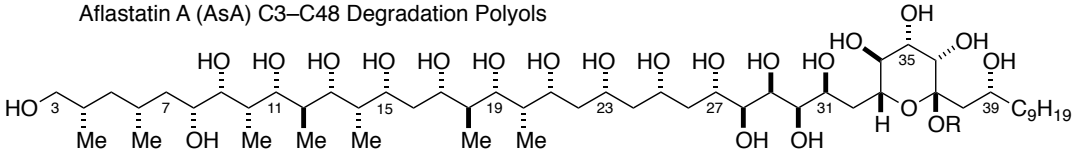


AsA #	Natural "1a"[a]	Natural 3a[f]	Synthetic 1a[b]	AsA #	Natural "1a"[a]	Natural 3a[f]	Synthetic 1a[b]
3	3.80		3.80	**28**	4.34[c]	4.30	4.30
	3.61		3.61	**29**	4.96	5.03	5.03
4	1.98		1.99	**30**	4.49	4.57	4.58
5	1.78		1.77	**31**	4.92	4.98	4.97
	1.04		1.05	**32**	3.17	3.21	3.21
6	2.14		2.15		2.49	2.55	2.56
7	1.84		1.83	**33**	4.24	4.85	4.85
	1.75		1.74	**34**	4.32	4.39	4.38
8	4.29		4.29	**35**	4.56	4.76	4.76
9	4.00		4.00	**36**	4.64	4.48	4.48
10	2.31		2.31	**37**			
11	4.32		4.32	**38**	2.45	2.14	2.14
12	2.08		2.08		2.19	2.74	2.73
13	4.12		4.12	**39**	4.18	4.72	4.72
14	1.97		1.95	**40**	1.67	1.66	1.65
15	4.49		4.48		1.59	1.52	1.51
16	2.04		2.04	**41**	1.59	1.54	1.51
	1.95		1.96		1.48	1.54	1.35
17	4.61		4.61	**42**	1.25	1.18	1.16
18	2.19		2.21	**43**	1.19	1.18	1.16
19	4.05		4.06	**44**	1.19		1.16
20	1.86		1.87	**45**	1.19		1.16
21	4.42	4.48	4.43	**46**	1.19		1.16
22	2.04	1.89	2.04	**47**	1.23		1.22
	1.86	1.89	1.86	**48**	0.83		0.83
23	4.49	4.52	4.48	**49**	1.10		1.10
24	2.05	2.02	2.03	**50**	1.07		1.06
	1.98	2.02	2.03	**51**	1.28		1.27
25	4.67	4.62	4.62	**52**	0.81		0.80
26	2.59	2.60	2.60	**53**	1.23		1.24
	2.14	2.15	2.16	**54**	0.97		0.97
27	4.67[c]	4.66	4.68	**55**	1.19		1.20

[d] Tabulated values in grey are $|\Delta\delta| \leq \pm 0.03$ ppm.

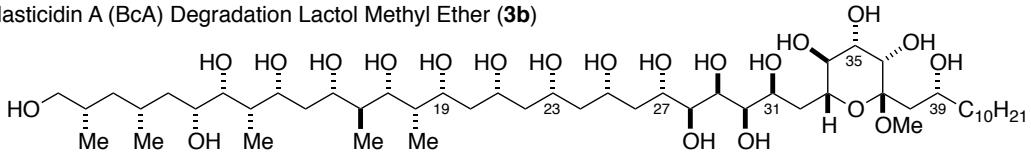
Table 9. Comparison of ^{13}C-NMR Data for Naturally Derived Aflastatin A (AsA) C3–C48 Degradation Polyol **1a**, Blasticidin (BcA) Degradation Lactol Methyl Ether **3b**, and Aflastatin A (AsA) C3–C48 Degradation Lactol Methyl Ethers **1b** and **1c**.[d]

Aflastatin A (AsA) C3–C48 Degradation Polyols



Lactol **1a**, R = H
Lactol Methyl Ether **1b**, R = Me
Lactol Trideuteriomethyl Ether **1c**, R = CD_3

Blasticidin A (BcA) Degradation Lactol Methyl Ether (**3b**)



AsA #	Natural "1a"[a]	Natural 3b[e]	Synthetic 1b[b]	Synthetic 1c[b]
3	67.2		67.3	67.2
4	34.0		34.0	34.0
5	41.6		41.6	41.6
6	27.8		27.9	27.8
7	42.3		42.4	42.3
8	69.5		69.5	69.5
9	77.9		78.0	77.9
10	38.1		38.1	38.1
11	78.8		78.9	78.8
12	38.8		38.8	38.8
13	81.6		81.6	81.6
14	39.3		39.5	39.5
15	77.1		77.1	77.1
16	45.7		45.8	45.7
17	73.9		74.0	73.9
18	42.7		42.8	42.7
19	78.8		78.9	78.7
20	39.5		39.5	39.5
21	76.2		76.3	76.2
22	42.7		42.8	42.7
23	70.8		70.9	70.8
24	36.9		37.0	36.9
25	73.1[f]	71.2	71.1	71.1
26	42.1	42.1	42.1	42.1
27	72.2[c]	72.2	72.2	72.2
28	76.2[c]	76.2	76.3	76.2

Table 9 (Continued). Comparison of ^{13}C-NMR Data for Naturally Derived Aflastatin A (AsA) C3–C48 Degradation Polyol **1a**, Blasticidin (BcA) Degradation Lactol Methyl Ether **3b**, and Aflastatin A (AsA) C3–C48 Degradation Lactol Methyl Ethers **1b** and **1c**.[d]

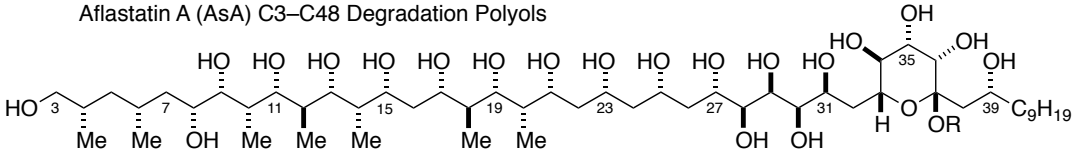
AsA #	Natural "1a"[a]	Natural 3b[e]	Synthetic 1b[b]	Synthetic 1c[b]
29	71.5	71.5	71.5	71.5
30	75.4	75.4	75.5	75.4
31	70.9	70.8	70.9	70.9
32	37.5	37.6	37.6	37.5
33	72.8	72.8	72.8	72.7
34	72.3	72.4	72.4	72.3
35	72.6	72.6	72.6	72.6
36	71.5[f]	73.1	73.1	73.0
37	103.2	103.3	103.3	103.2
38	39.3	39.4	39.4	39.3
39	66.9	66.9	66.9	66.9
40	39.3	39.4	39.4	39.3
41	26.0		26.0	26.0
42	29.8		29.8	29.8
43	30.0		30.0	29.9
44	30.0		30.0	30.0
45	29.5		29.5	29.5
46	32.0		32.1	32.0
47	22.9		22.9	22.9
48	14.2		14.3	14.2
49	18.6		18.7	18.6
50	21.7		21.7	21.6
51	8.3		8.3	8.3
52	13.2		13.2	13.2
53	6.4		6.4	6.4
54	11.6		11.7	11.6
55	6.1		6.1	6.1
56	n/a	47.8	47.8	n/a

[d] All tabulated values (except those shaded in grey) are $|\Delta\delta| \leq \pm 0.2$ ppm.

[f] Values shaded in grey correspond to those originally reported in 2000. In 2007, the chemical shift of C25 was revised from 73.1 ppm to 71.1 ppm. However, we believe the chemical shift of 71.5 ppm originally reported for C36 should instead be revised to 71.1 ppm. Then, the data for these two atoms should be switched. We noted a similar switch of NMR data for C27 and C28 in the 2007 paper (see note *c*).

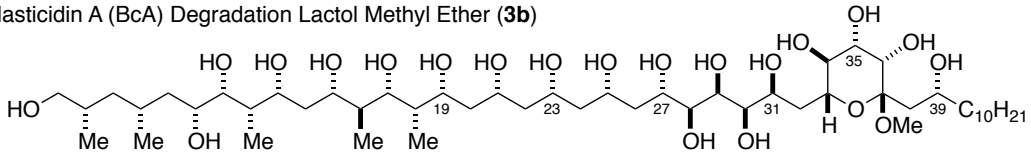
Table 10. Comparison of ^{1}H-NMR Data for Naturally Derived Aflastatin A (AsA) C3–C48 Degradation Polyol **1a**, Blasticidin (BcA) Degradation Lactol Methyl Ether **3b**, and Aflastatin A (AsA) C3–C48 Degradation Lactol Methyl Ethers **1b** and **1c**.[d]

Aflastatin A (AsA) C3–C48 Degradation Polyols



Lactol **1a**, R = H
Lactol Methyl Ether **1b**, R = Me
Lactol Trideuteriomethyl Ether **1c**, R = CD_3

Blasticidin A (BcA) Degradation Lactol Methyl Ether (**3b**)



AsA #	Natural "1a"[a]	Natural 3b[e]	Synthetic 1b[b]	Synthetic 1c[b]
3	3.80		3.80	3.79
	3.61		3.61	3.60
4	1.98		1.98	1.98
5	1.78		1.77	1.76
	1.04		1.04	1.04
6	2.14		2.15	2.14
7	1.84		1.83	1.83
	1.75		1.75	1.74
8	4.29		4.28	4.28
9	4.00		4.00	4.00
10	2.31		2.30	2.30
11	4.32		4.31	4.31
12	2.08		2.08	2.08
13	4.12		4.12	4.11
14	1.97		1.96	1.96
15	4.49		4.50	4.49
16	2.04		2.04	2.03
	1.95		1.96	1.96
17	4.61		4.62	4.62
18	2.19		2.21	2.21
19	4.05		4.05	4.05
20	1.86		1.87	1.87
21	4.42		4.42	4.42
22	2.04		2.04	2.03
	1.86		1.85	1.85
23	4.49		4.50	4.49
24	2.05		2.04	2.03
	1.98		1.98	1.98
25	4.67[f]	4.63	4.64	4.64
26	2.59	2.16	2.60	2.59
	2.14	2.16	2.17	2.16
27	4.67[c]	4.68	4.67	4.67
28	4.34[c]	4.33	4.34	4.34

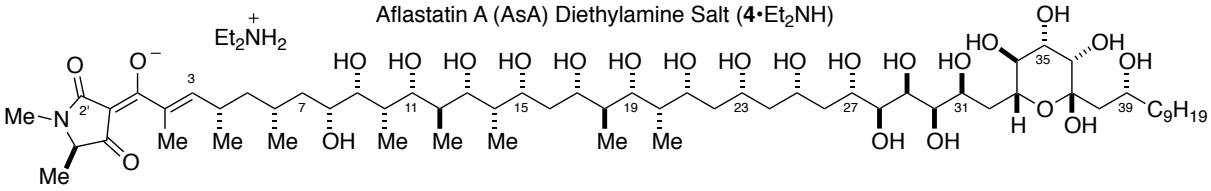
Table 10 (Continued). Comparison of ^{1}H-NMR Data for Naturally Derived Aflastatin A (AsA) C3–C48 Degradation Polyol **1a**, Blasticidin (BcA) Degradation Lactol Methyl Ether **3b**, and Aflastatin A (AsA) C3–C48 Degradation Lactol Methyl Ethers **1b** and **1c**.[d]

AsA #	Natural "1a"[a]	Natural 3b[e]	Synthetic 1b[b]	Synthetic 1c[b]
29	4.96	4.97	4.96	4.97
30	4.49	4.50	4.50	4.49
31	4.92	4.93	4.93	4.92
32	3.17	3.18	3.17	3.17
	2.49	2.49	2.49	2.49
33	4.24	4.21	4.23	4.23
34	4.32	4.31	4.32	4.31
35	4.56	4.56	4.56	4.57
36	4.64[f]	4.66	4.67	4.67
37				
38	2.45	2.44	2.45	2.44
	2.19	2.22	2.20	2.20
39	4.18	4.18	4.19	4.18
40	1.67	1.68	1.67	1.67
	1.59	1.58	1.59	1.58
41	1.59		1.59	1.60
	1.48		1.47	1.47
42	1.25		1.24	1.24
43	1.19		1.19	1.18
44	1.19		1.19	1.18
45	1.19		1.19	1.18
46	1.19		1.19	1.18
47	1.23		1.22	1.22
48	0.83		0.83	0.83
49	1.10		1.10	1.10
50	1.07		1.06	1.06
51	1.28		1.28	1.28
52	0.81		0.80	0.80
53	1.23		1.24	1.23
54	0.97		0.97	0.97
55	1.19		1.19	1.19
56	n/a	3.35	3.35	n/a

[d] All tabulated values are $|\Delta\delta| \leq \pm 0.03$ ppm.

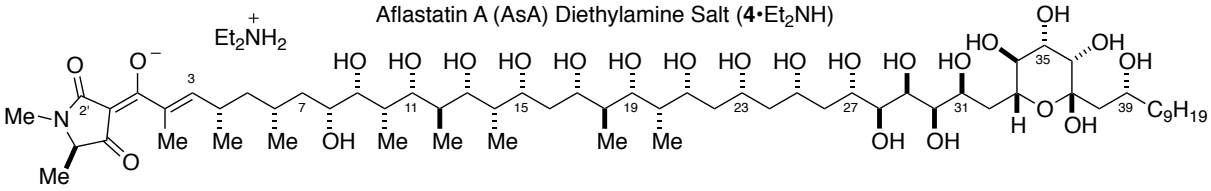
[f] As with the ^{13}C-NMR data (see Table S9), we believe that the resonances assigned to H25 and H36 (shaded in grey) should be switched. We noted a similar switch of NMR data for H27 and H28 in the 2007 paper (see note *c*).

Table 11. Comparison of ^{13}C-NMR Data for Naturally Derived and Synthetic Aflastatin A (AsA) Diethylamine Salt **4**•Et_2NH.



AsA #	Nat. 4•Et_2NH^g	Syn. 4•Et_2NH^h	AsA #	Nat. 4•Et_2NH^g	Syn. 4•Et_2NH^h
1	191.5	191.8	**29-OH**		
2	135.2	135.0	**30**	72.5	72.4
3	139.3	138.8	**30-OH**		
4	29.9	29.8	**31**	68.6	68.6
5	44.8	44.7	**31-OH**		
6	26.1	26.2	**32**	35.8	35.8
7	42.8	42.7	**33**	70.2	70.1
8	67.2	67.2	**34**	71.2	71.2
8-OH			**34-OH**		
9	75.0	74.9	**35**	70.7	70.7
9-OH			**35-OH**		
10	37.1	37.1	**36**	73.0	73.0
11	75.8	75.8	**36-OH**		
11-OH			**37**	98.4	98.4
12	38.1	38.0	**37-OH**		
13	78.9	79.0	**38**	41.6	41.8
13-OH			**39**	67.5	67.5
14	38.1	38.1	**39-OH**		
15	74.5	74.5	**40**	38.1	38.2
15-OH			**41**	24.9	24.9
16	34.9	34.8	**42**	29.2	29.2
17	70.4	70.2	**43**	29.0	29.0
17-OH			**44**	29.0	29.1
18	41.6	41.7	**45**	28.7	28.7
19	76.2	76.2	**46**	31.3	31.3
19-OH			**47**	22.1	22.1
20	38.1	38.2	**48**	13.9	14.0
21	73.5	73.5	**49**	13.3	13.4
21-OH			**50**	21.5	21.4
22	41.6	41.6	**51**	20.8	20.7
23	67.9	67.9	**52**	8.7	8.7
23-OH			**53**	12.8	12.8
24	44.5	44.5	**54**	6.4	6.4
25	68.6	68.6	**55**	10.6	10.5
25-OH			**56**	5.8	5.8
26	41.0	41.0	**2'**	173.4	173.5
27	69.7	69.7	**3'**	98.1	98.2
27-OH			**4'**	192.6	193.3
28	74.3	74.3	**5'**	59.4	59.4
28-OH			**6'**	15.9	15.9
29	69.4	69.3	**7'**	26.3	26.3

Table 12. Comparison of ^{1}H-NMR Data for Naturally Derived and Synthetic Aflastatin A (AsA) Diethylamine Salt **4**•Et_2NH.



AsA #	Nat. 4•Et_2NH^g	Syn. 4•Et_2NH^h	AsA #	Nat. 4•Et_2NH^g	Syn. 4•Et_2NH^h
1			**29-OH**	4.12	4.15
2			**30**	3.45	3.44
3	5.45	5.42	**30-OH**	4.17	4.17
4	2.54	2.53	**31**	3.83	3.85
5	1.34, 0.93	1.33, 0.94	**31-OH**	4.12	4.17
6	1.90	1.88	**32**	2.06, 1.48	2.05, 1.46
7	1.26	1.25	**33**	3.62	3.62
8	3.64	3.64	**34**	3.18	3.17
8-OH	n/a	5.02	**34-OH**	n/a	4.64
9	3.26	3.26	**35**	3.56	3.56
9-OH	n/a	4.42	**35-OH**	n/a	4.40
10	1.81	1.81	**36**	3.41	3.39
11	3.71	3.68	**36-OH**	4.45	4.49
11-OH	5.20	5.19	**37**		
12	1.62	1.61	**37-OH**	6.11	6.13
13	3.67	3.69	**38**	1.82, 1.42	1.82, 1.41
13-OH	5.26	5.27	**39**	3.89	3.86
14	1.67	1.66	**39-OH**	4.75	4.85
15	3.85	3.86	**40**	1.30	1.30
15-OH	4.79	4.80	**41**	1.23	1.23
16	1.60, 1.30	1.61, 1.30	**42**	1.23	1.23
17	3.91	3.90	**43**	1.23	1.23
17-OH	4.71	4.72	**44**	1.23	1.23
18	1.65	1.65	**45**	1.23	1.23
19	3.46	3.44	**46**	1.23	1.23
19-OH	4.57	4.60	**47**	1.23	1.23
20	1.53	1.53	**48**	0.84	0.84
21	3.81	3.79	**49**	1.67	1.69
21-OH	4.76	4.75	**50**	0.88	0.88
22	1.53	1.53	**51**	0.85	0.85
23	3.79	3.76	**52**	0.84	0.84
23-OH	4.73	4.79	**53**	0.64	0.64
24	1.55, 1.39	1.56, 1.40	**54**	0.81	0.81
25	3.87	3.87	**55**	0.68	0.68
25-OH	5.24	5.28	**56**	0.79	0.78
26	1.85, 1.35	1.83, 1.33	**2'**		
27	3.63	3.62	**3'**		
27-OH	4.66	4.71	**4'**		
28	3.25	3.26	**5'**	3.20	3.24
28-OH	4.59	4.62	**6'**	1.11	1.12
29	3.82	3.85	**7'**	2.68	2.70

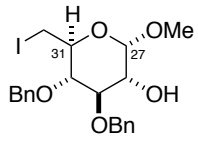
Appendix

2

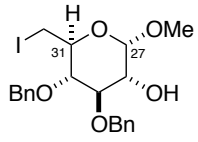
^{1}H- and ^{13}C-NMR Spectra

Chapter 3

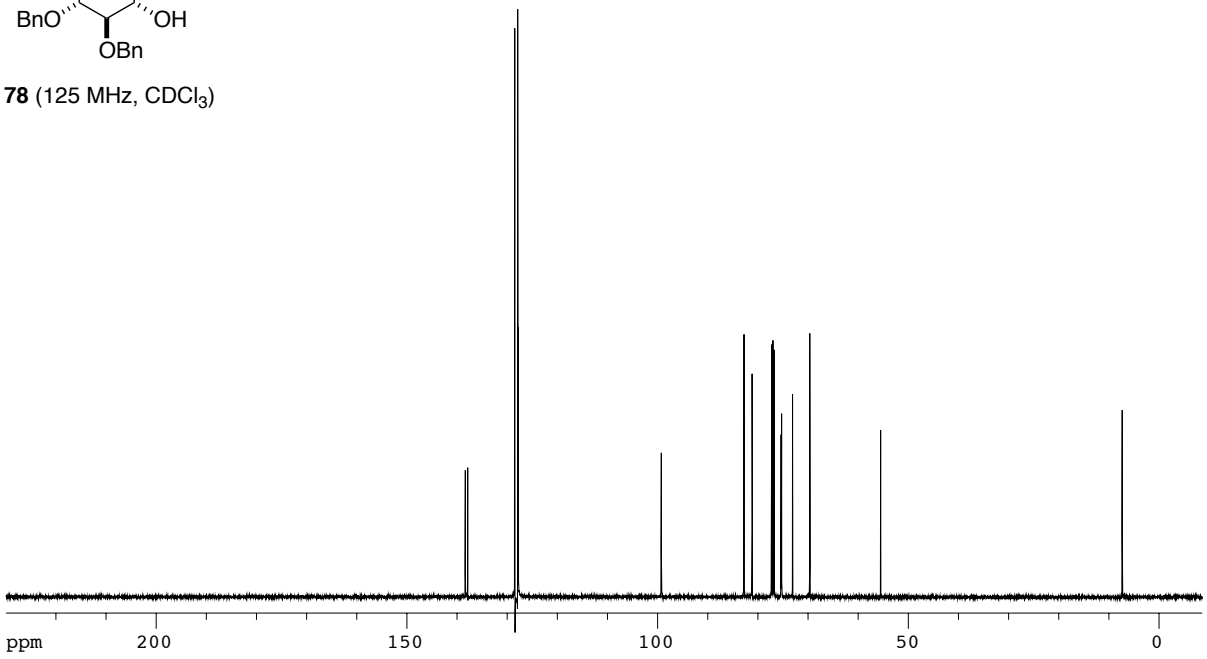
Compound 78.



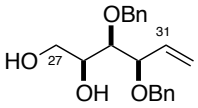
78 (600 MHz, $CDCl_3$)



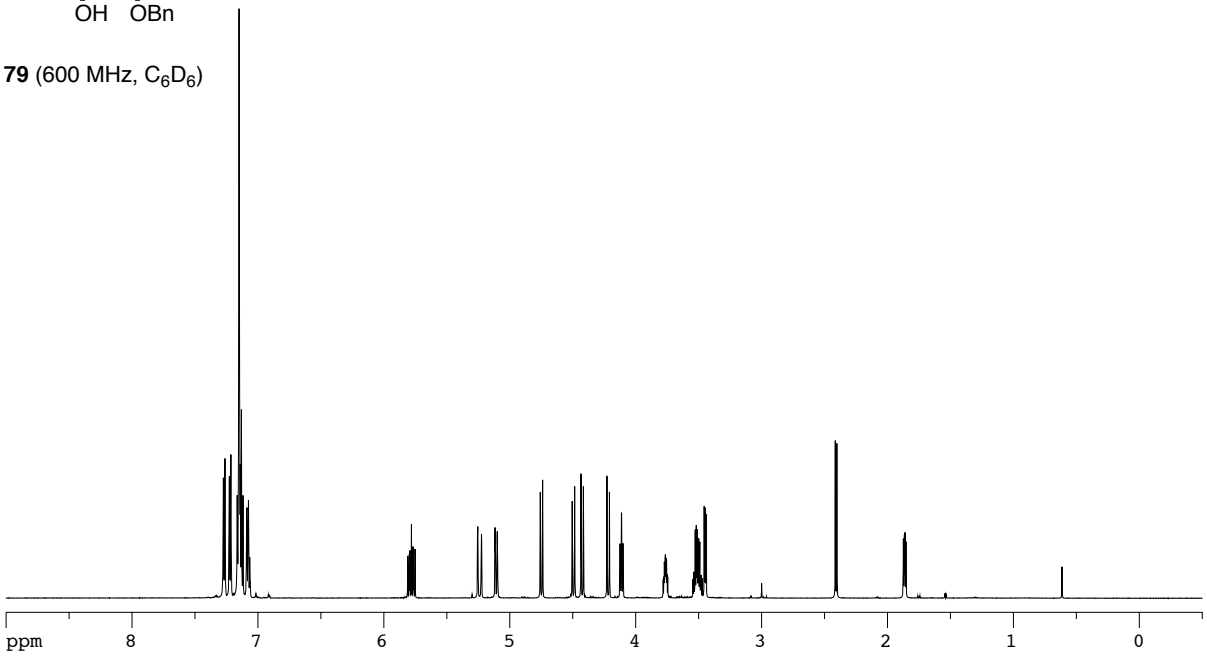
78 (125 MHz, $CDCl_3$)

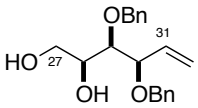


Compound 79.



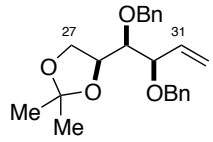
79 (600 MHz, C_6D_6)



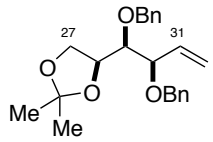


79 (125 MHz, C_6D_6)

Compound 63.

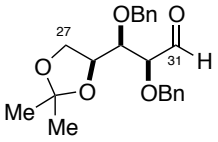


63 (600 MHz, $CDCl_3$)

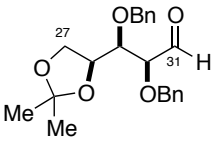


63 (125 MHz, $CDCl_3$)

Compound 80.

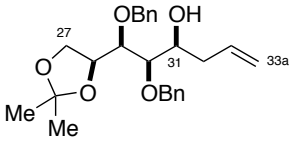


80 (600 MHz, C_6D_6)

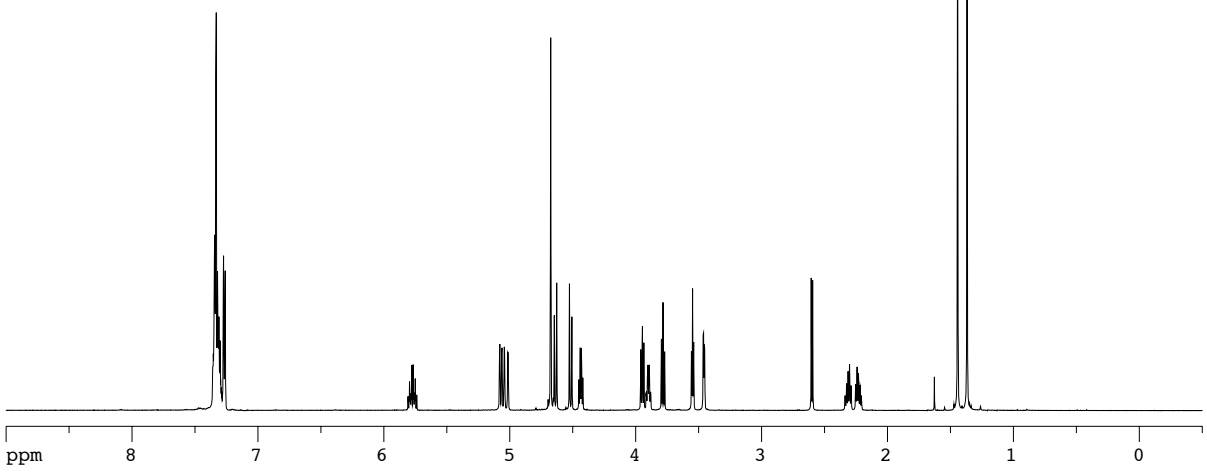


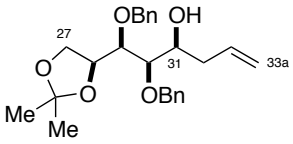
80 (125 MHz, C_6D_6)

Compound 64.



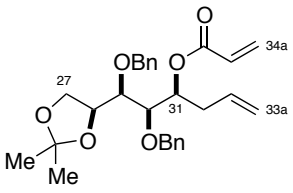
64 (600 MHz, $CDCl_3$)



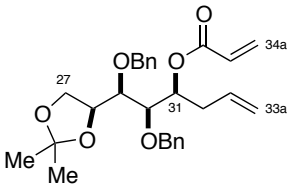


64 (125 MHz, $CDCl_3$)

Compound 81.

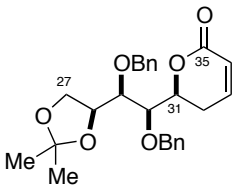


81 (600 MHz, $CDCl_3$)

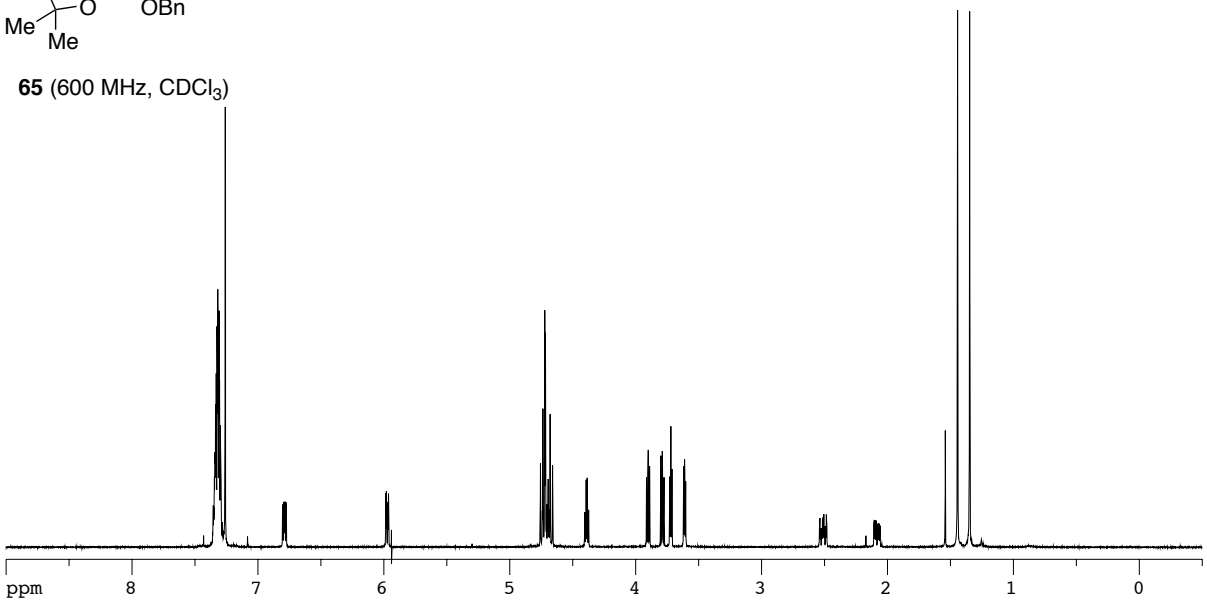


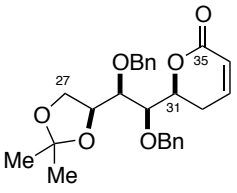
81 (125 MHz, $CDCl_3$)

Compound 65.



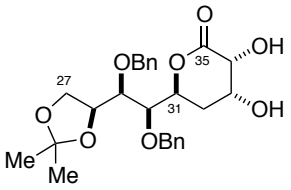
65 (600 MHz, $CDCl_3$)



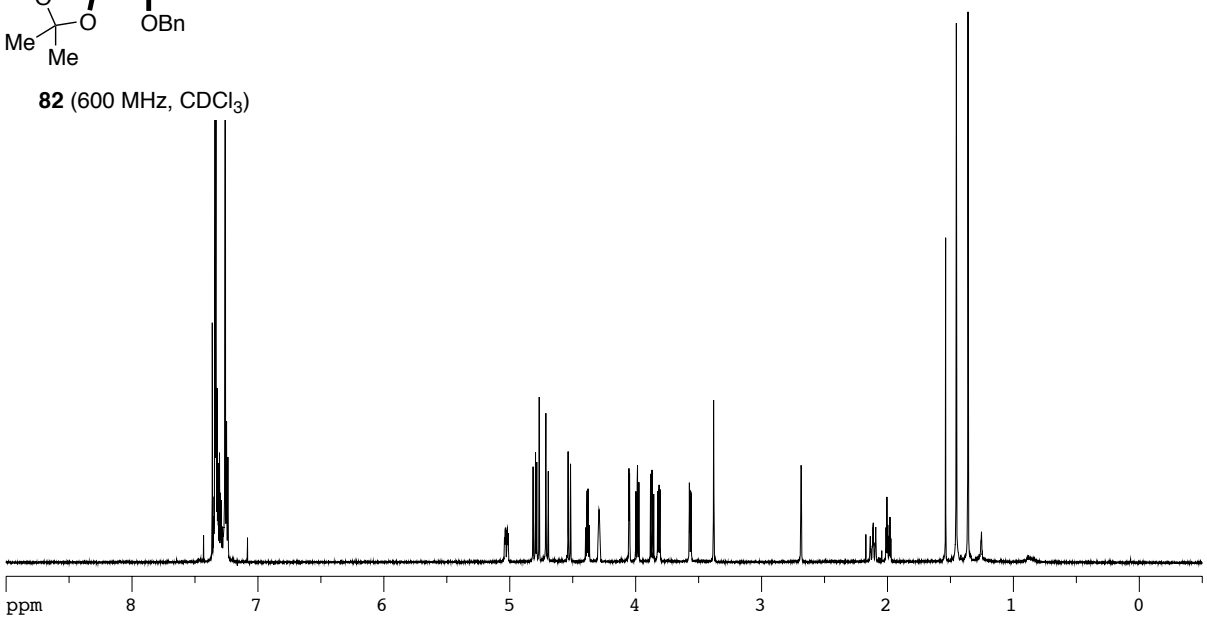


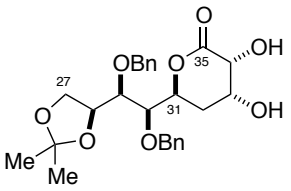
65 (125 MHz, $CDCl_3$)

Compound 82.



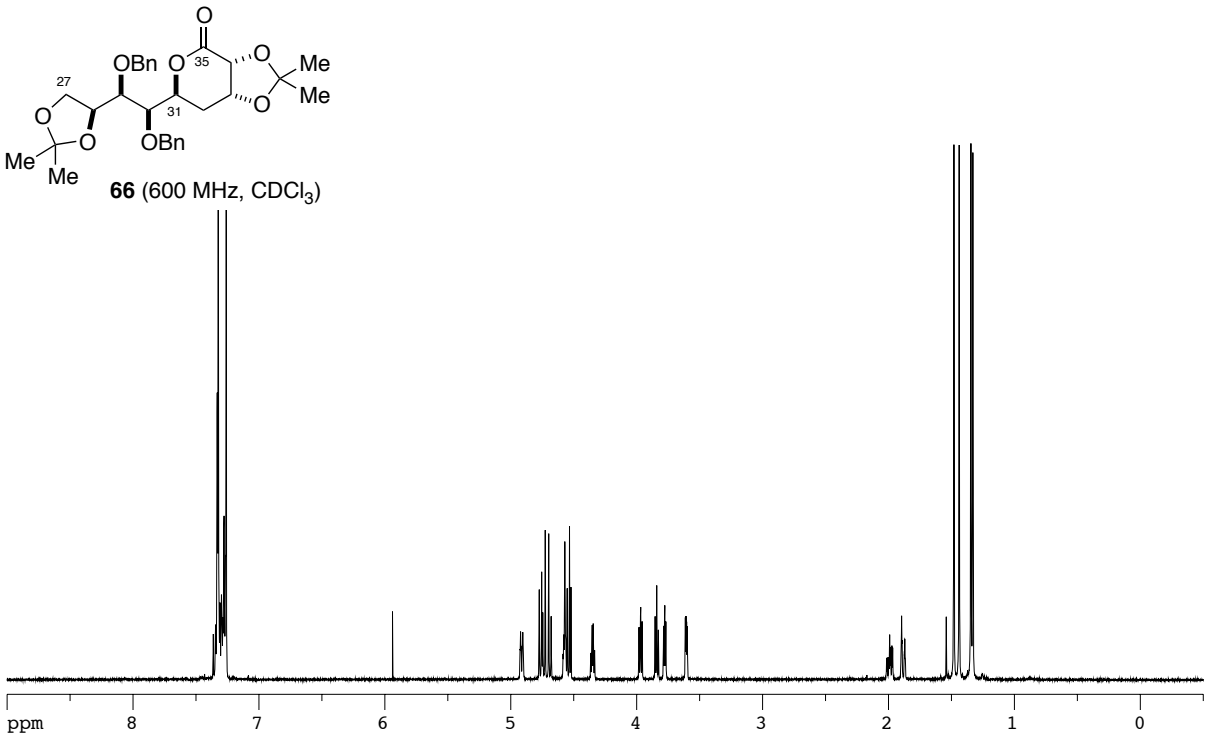
82 (600 MHz, $CDCl_3$)

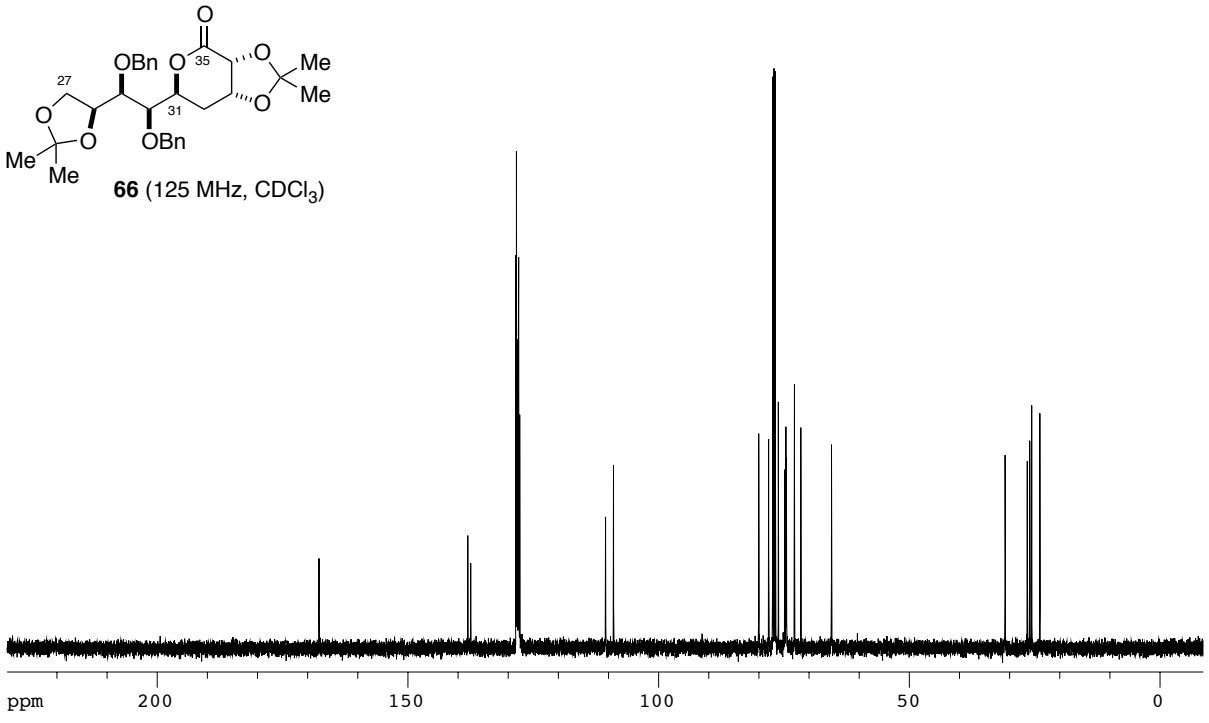




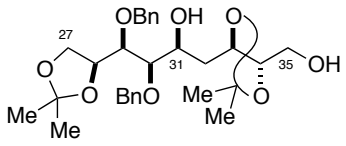
82 (125 MHz, $CDCl_3$)

Compound 66.

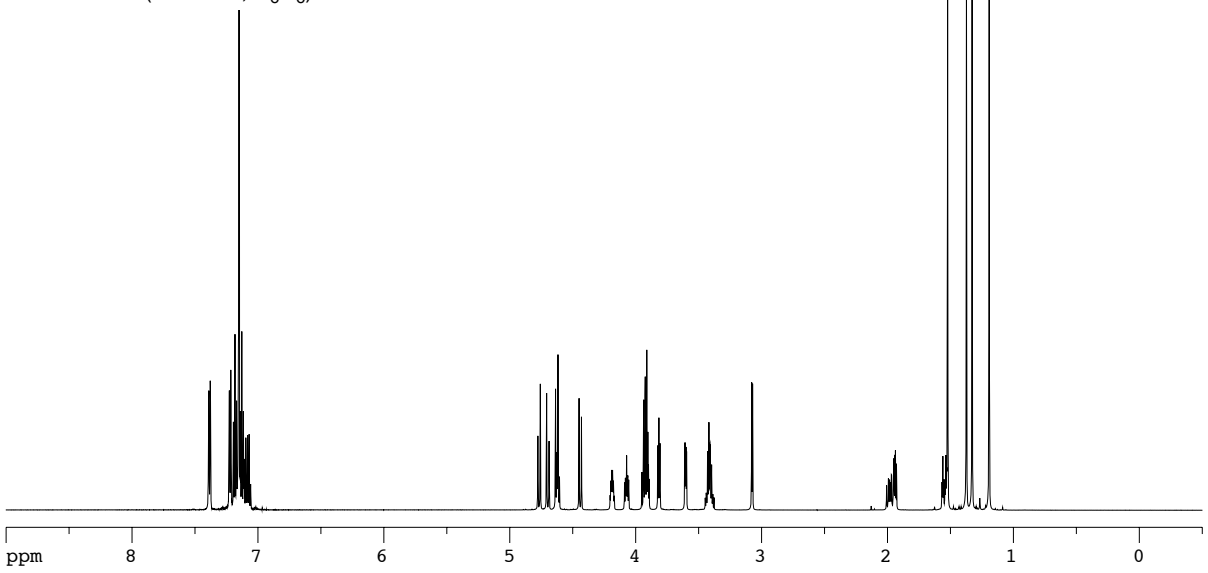

O
OBn
O
35
O
Me
Me
27
O
31
O
O
OBn
Me
Me
66 (600 MHz, CDCl3)
ppm
8
7
6
5
4
3
2
1
0

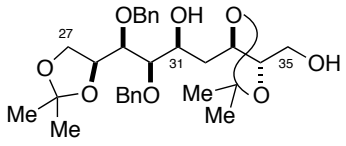

O
OBn
O
35
O
Me
Me
27
O
31
O
O
OBn
Me
Me
66 (125 MHz, CDCl3)
ppm
200
150
100
50
0

Compound 83.



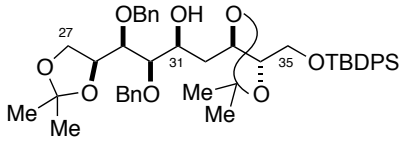
83 (600 MHz, C_6D_6)



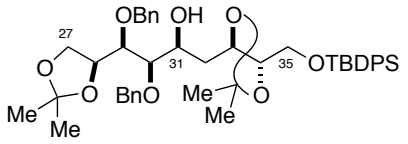


83 (125 MHz, C_6D_6)

Compound 84.

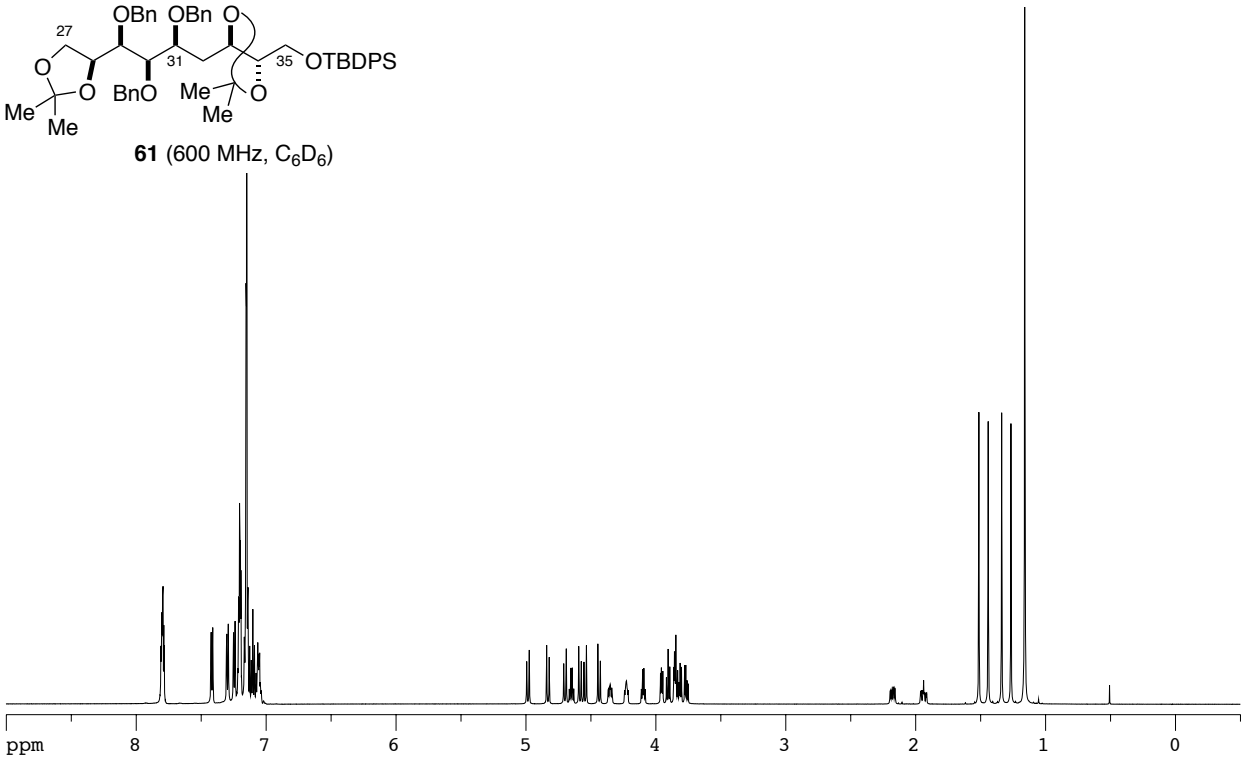


84 (600 MHz, $CDCl_3$)

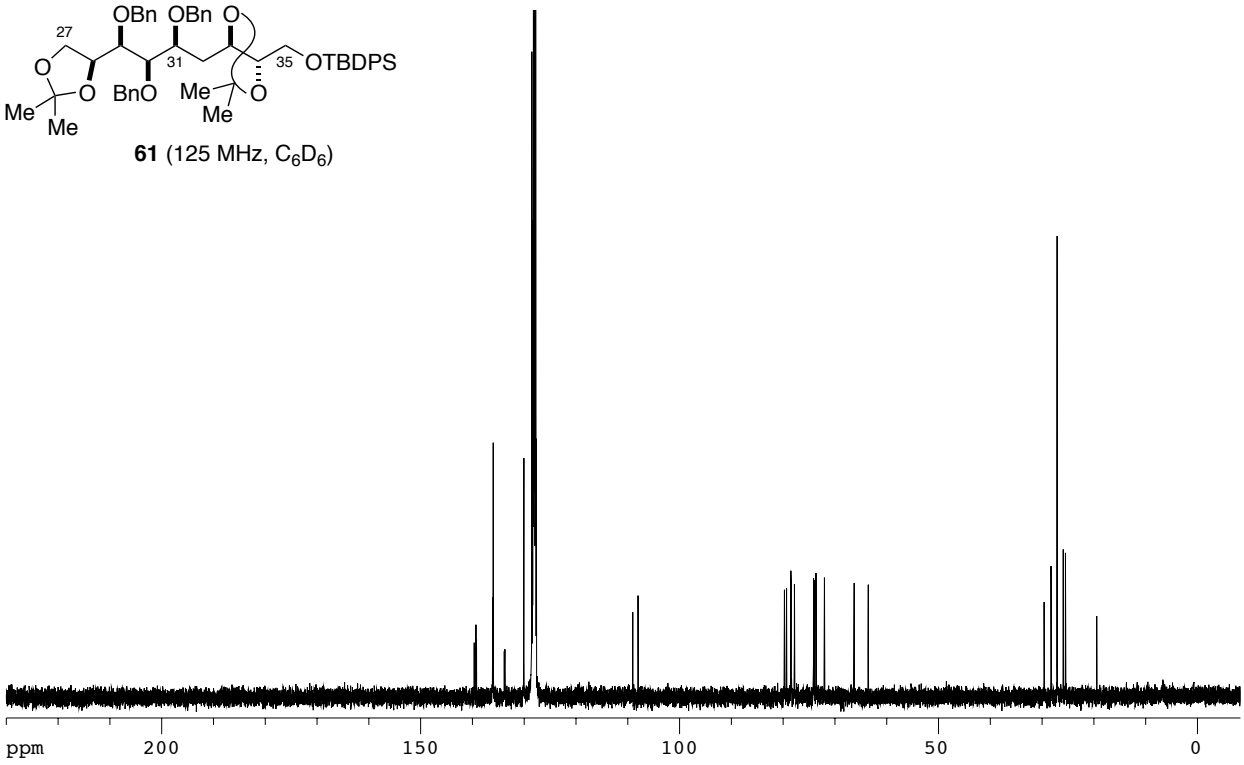


84 (125 MHz, $CDCl_3$)

Compound 61.

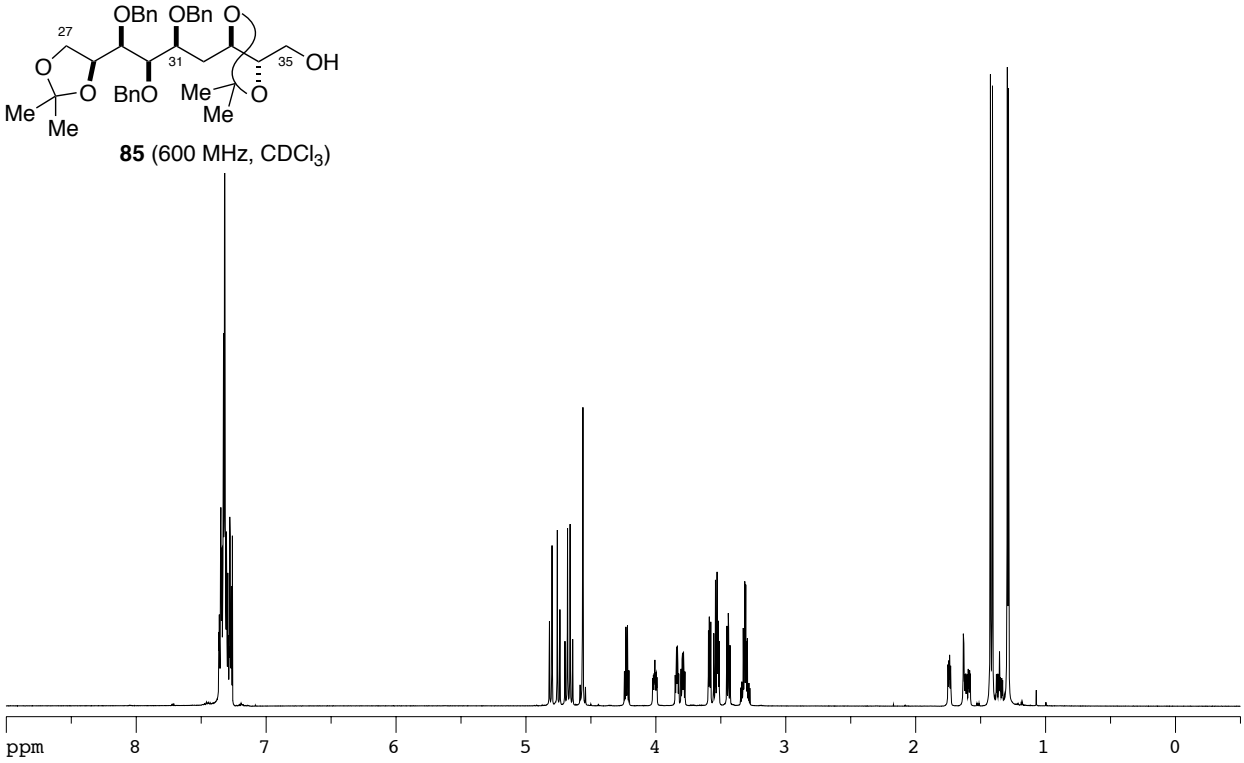


61 (600 MHz, C_6D_6)

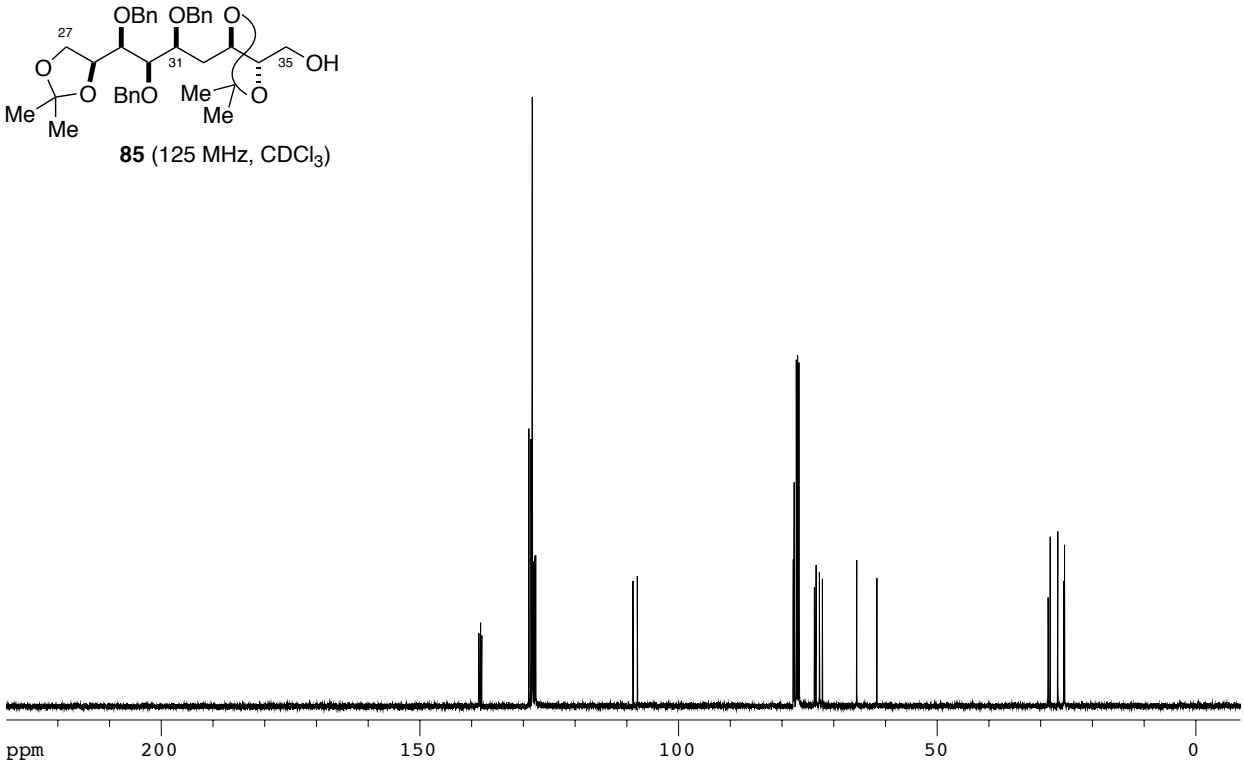


61 (125 MHz, C_6D_6)

Compound 85.

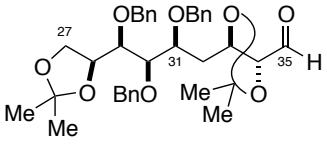


85 (600 MHz, $CDCl_3$)

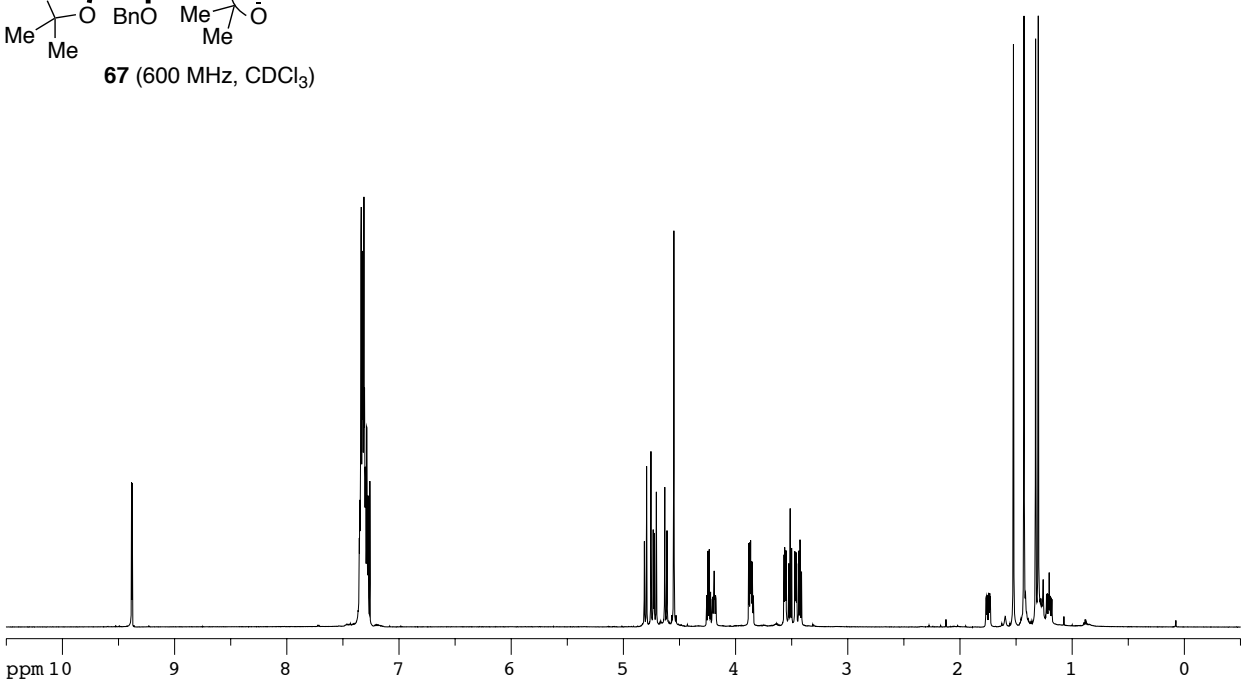


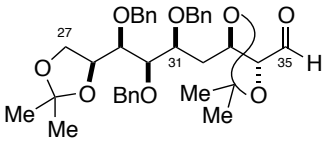
85 (125 MHz, $CDCl_3$)

Compound 67.



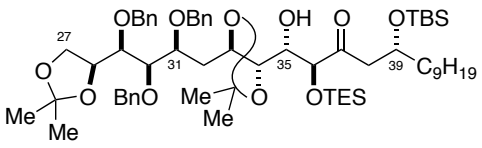
67 (600 MHz, $CDCl_3$)



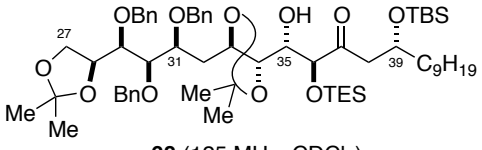


67 (125 MHz, $CDCl_3$)

Compound 68.

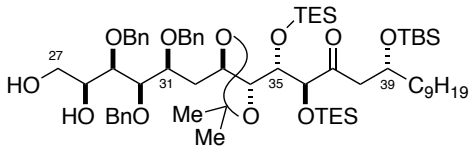


68 (600 MHz, $CDCl_3$)

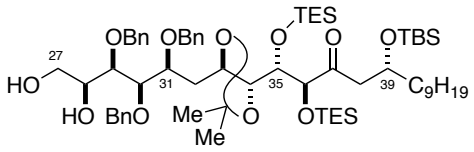


68 (125 MHz, $CDCl_3$)

Compound 69.

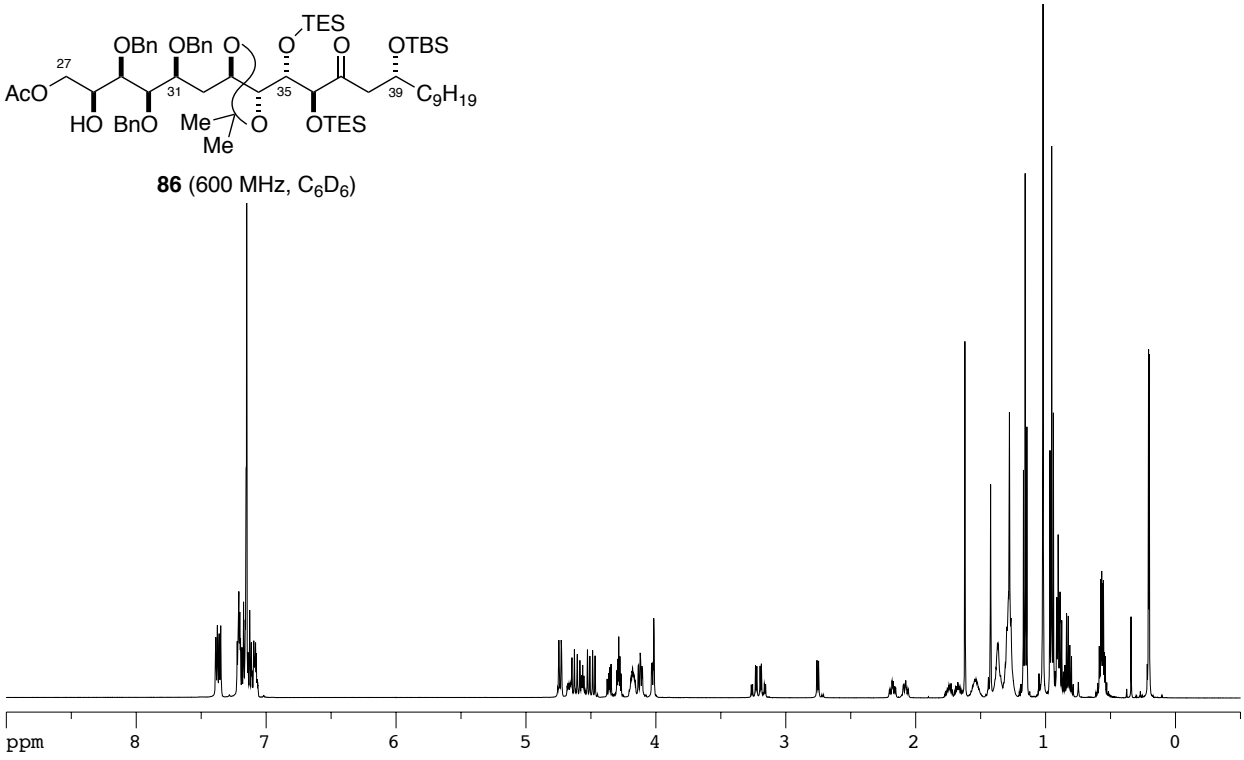


69 (600 MHz, C_6D_6)

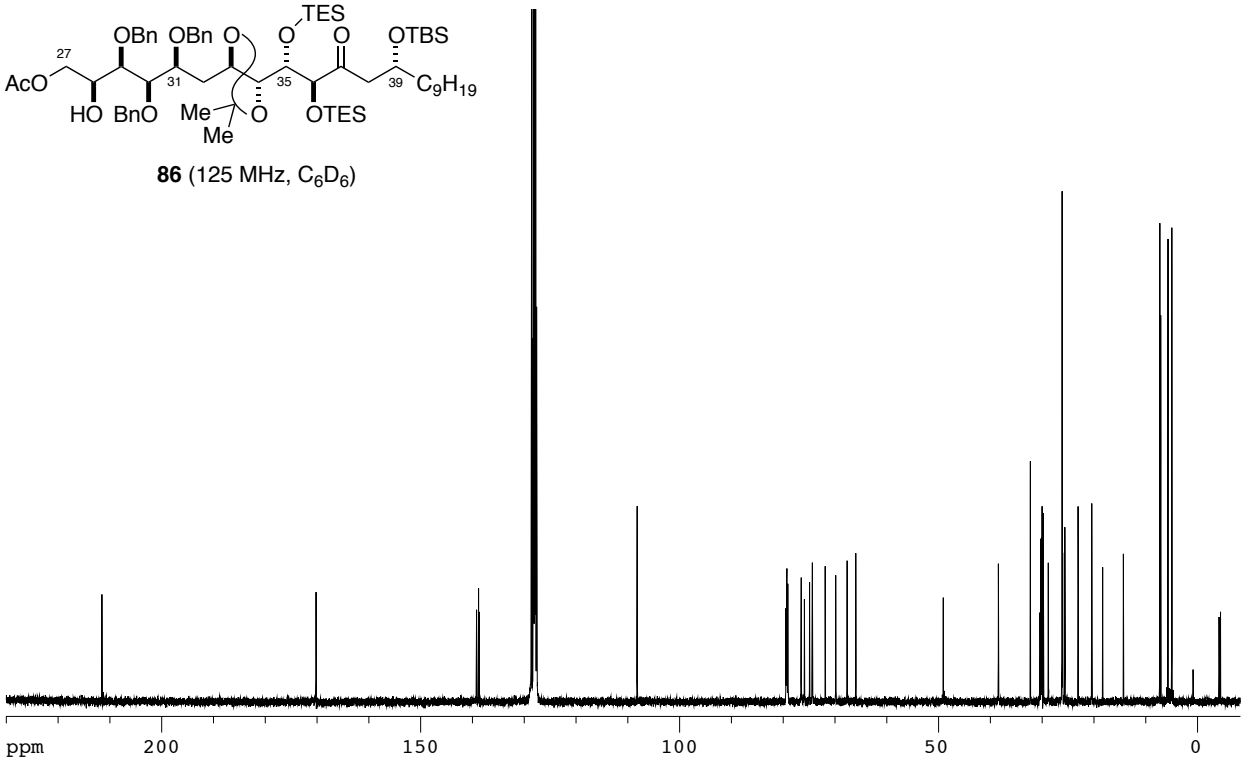


69 (125 MHz, C_6D_6)

Compound 86.

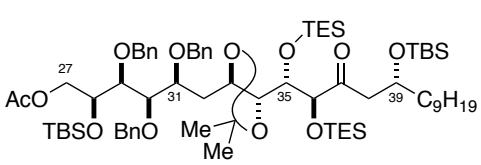


86 (600 MHz, C_6D_6)

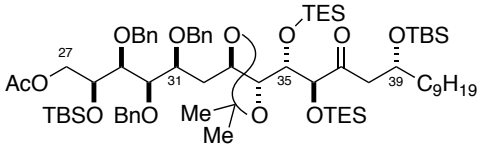


86 (125 MHz, C_6D_6)

Compound 70.

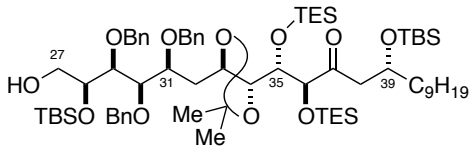


70 (600 MHz, $CDCl_3$)

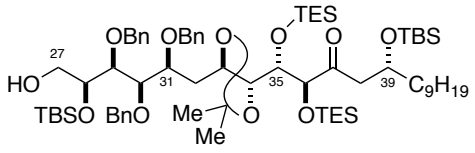


70 (100 MHz, $CDCl_3$)

Compound 87.

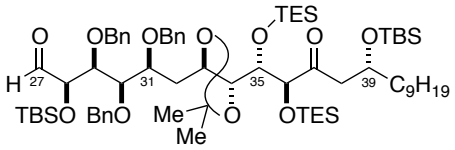


87 (600 MHz, $CDCl_3$)

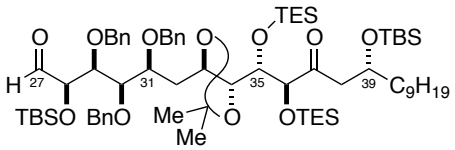


87 (125 MHz, $CDCl_3$)

Compound 71.



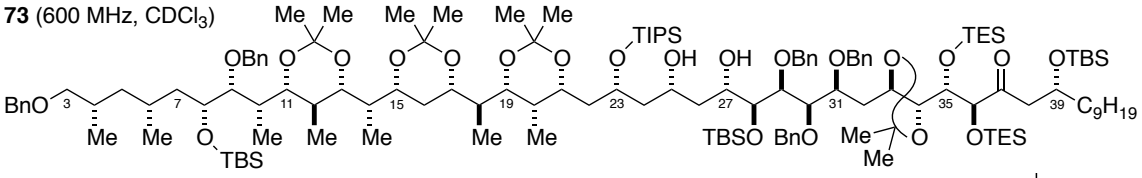
71 (600 MHz, $CDCl_3$)

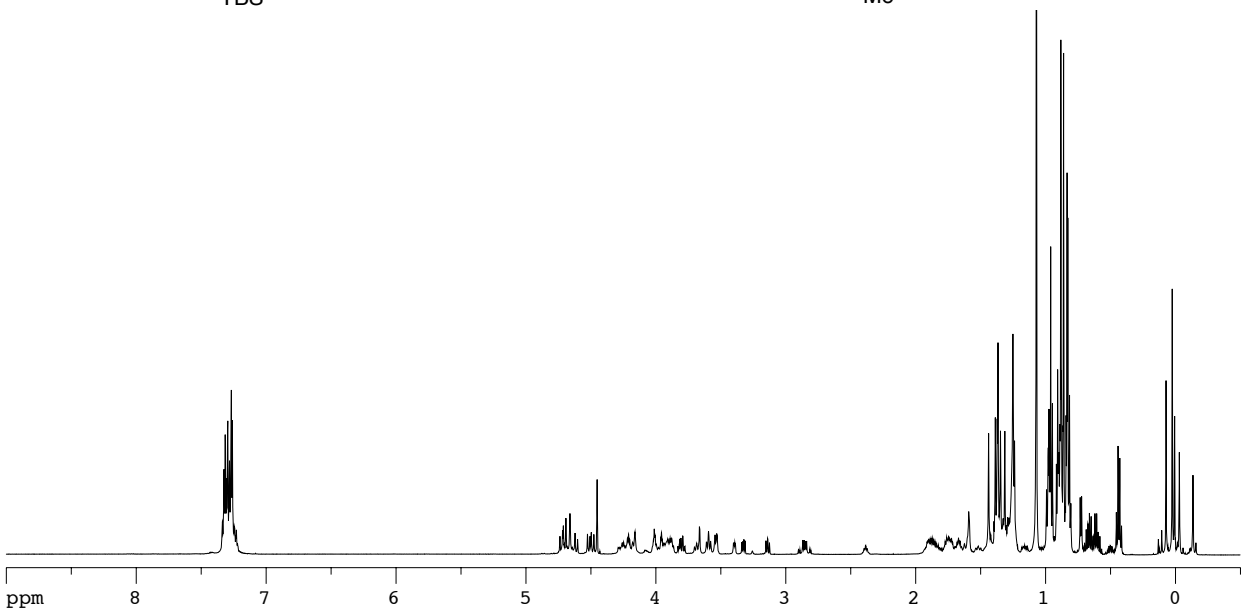


71 (125 MHz, $CDCl_3$)

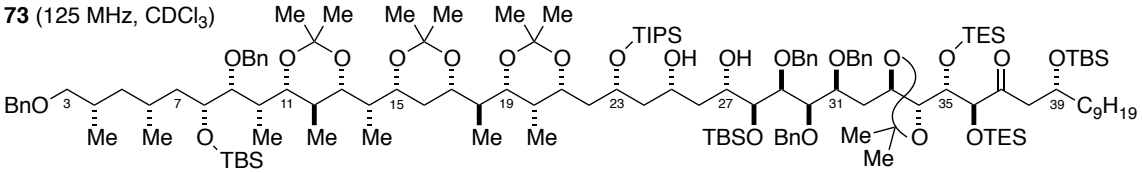
Compound 73.

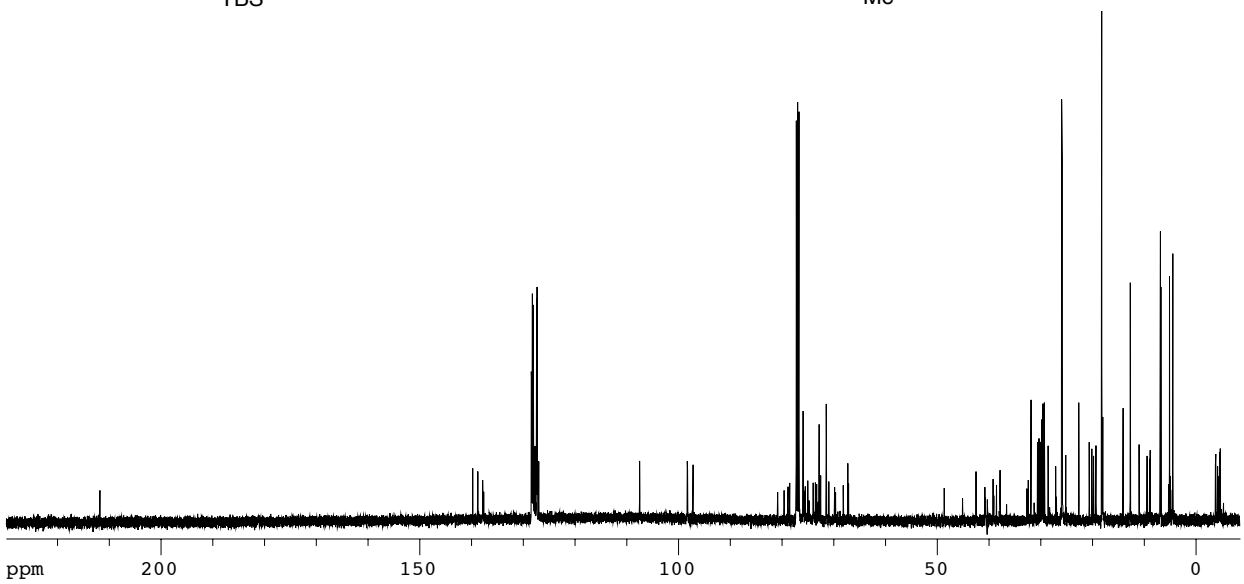
73 (600 MHz, $CDCl_3$)





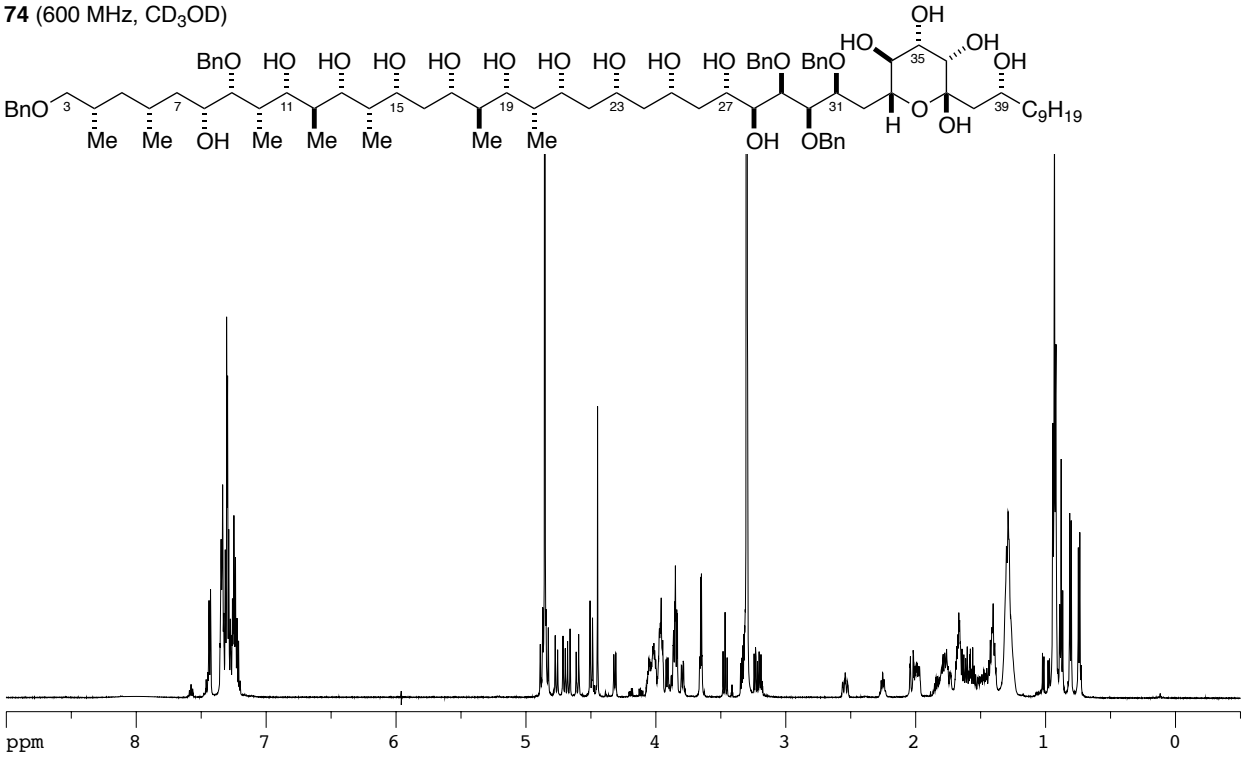
73 (125 MHz, $CDCl_3$)



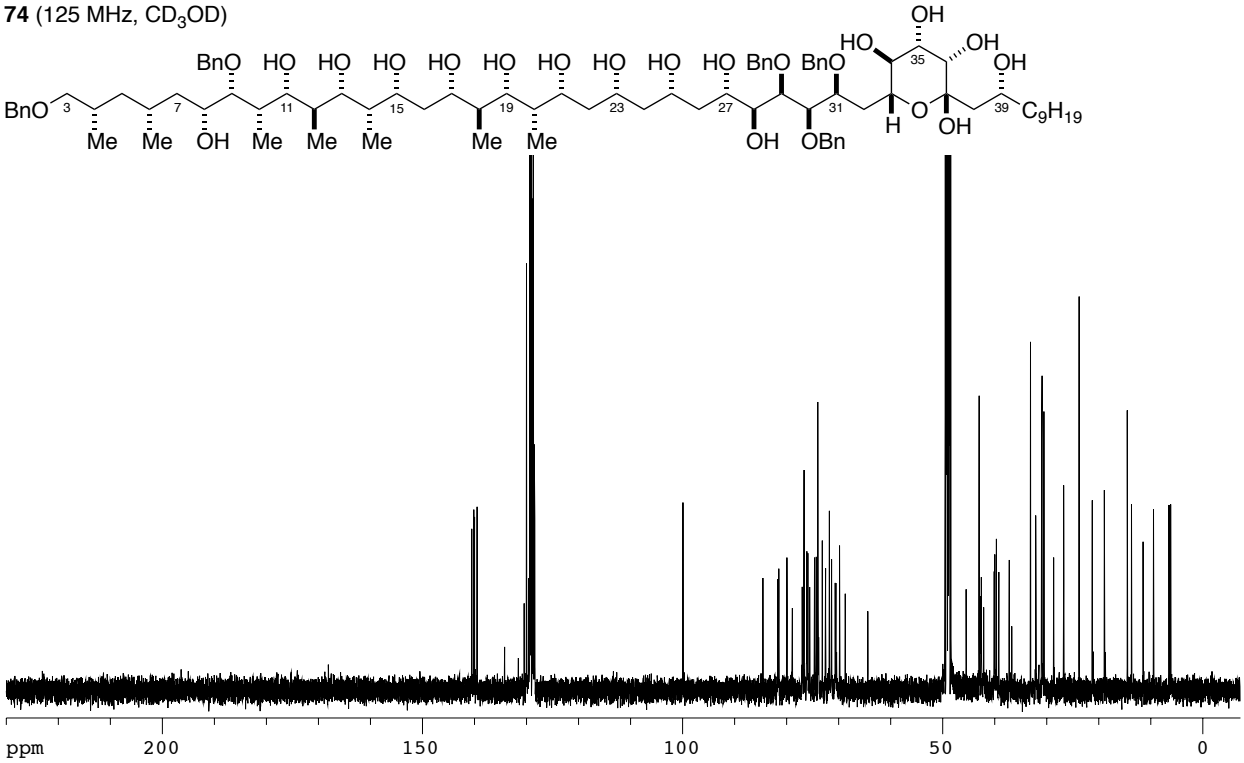


Compound 74.

74 (600 MHz, CD_3OD)

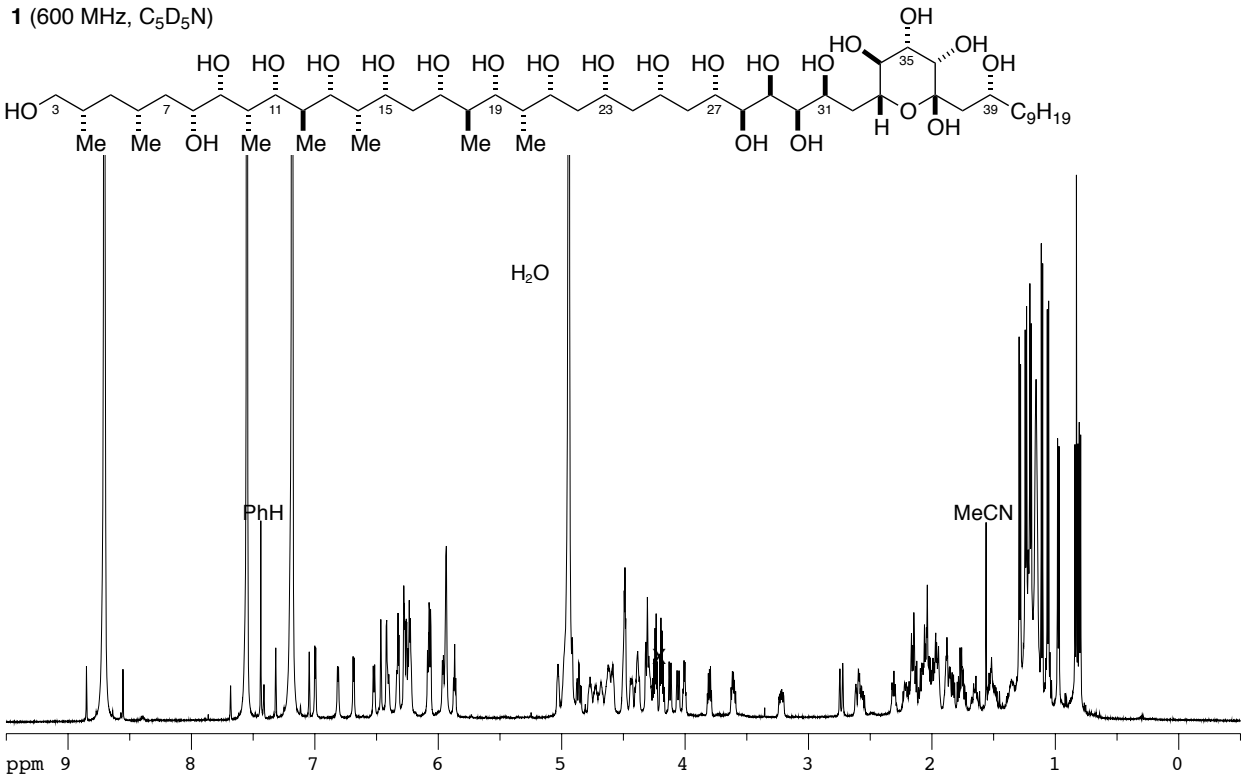


74 (125 MHz, CD_3OD)

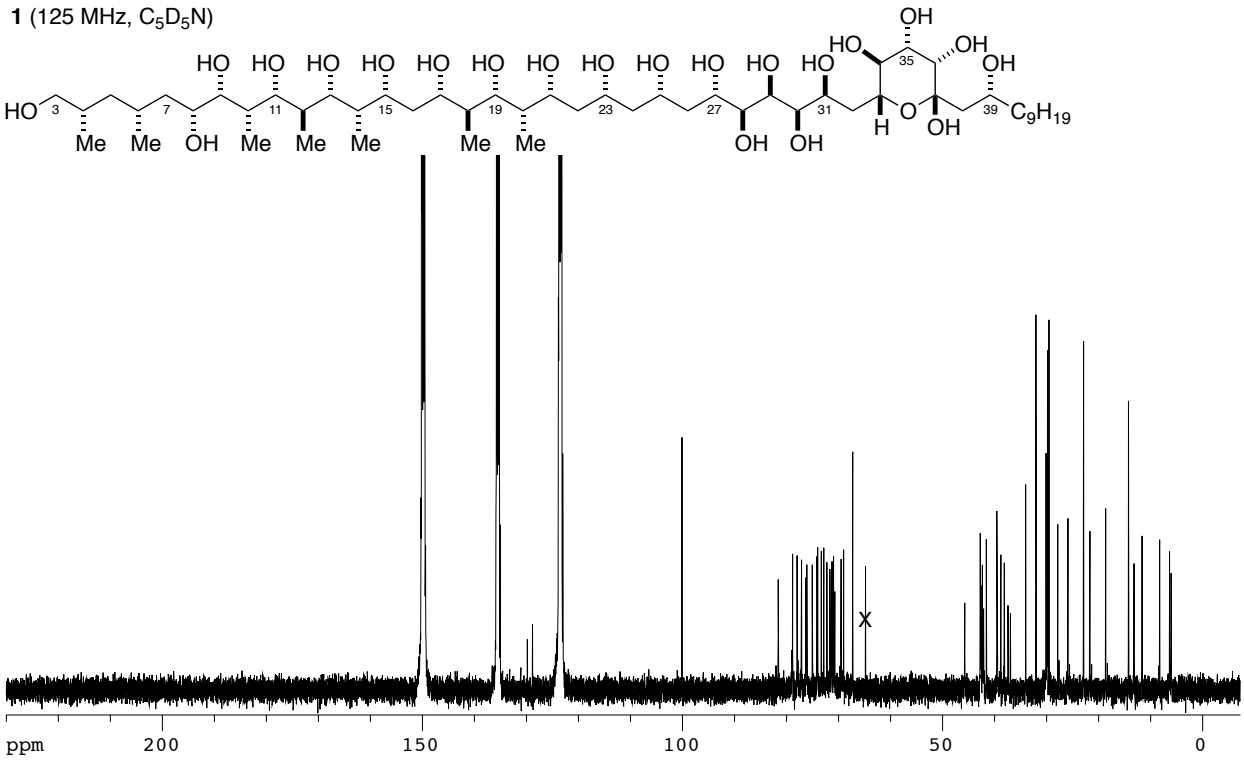


Compound 1.

1 (600 MHz, C_5D_5N)

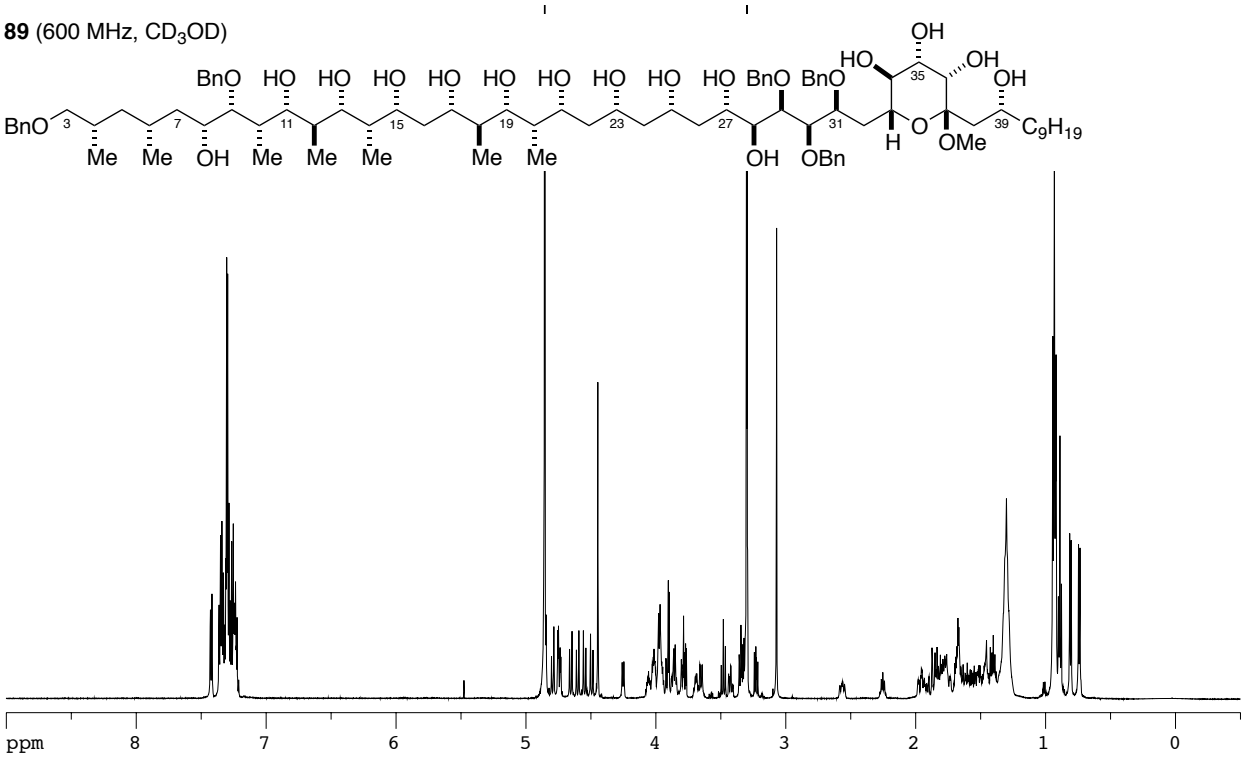


1 (125 MHz, C_5D_5N)

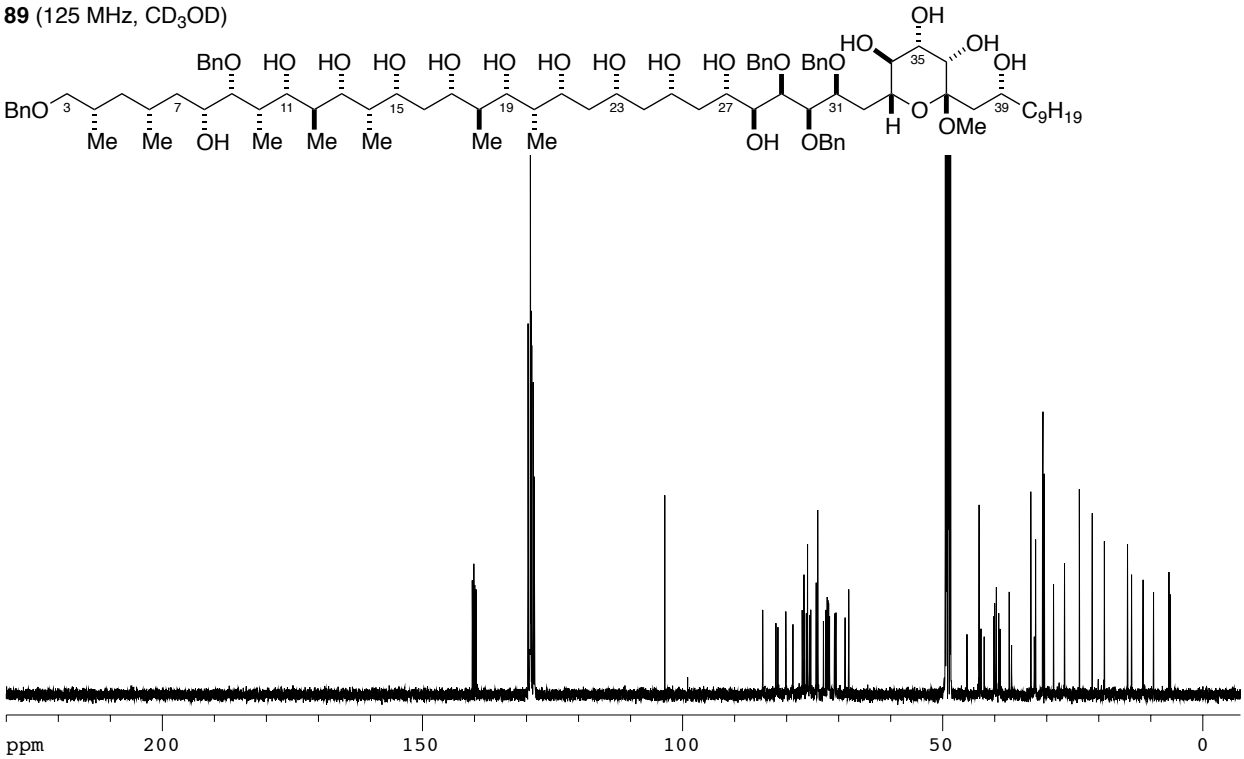


Compound 89.

89 (600 MHz, CD_3OD)

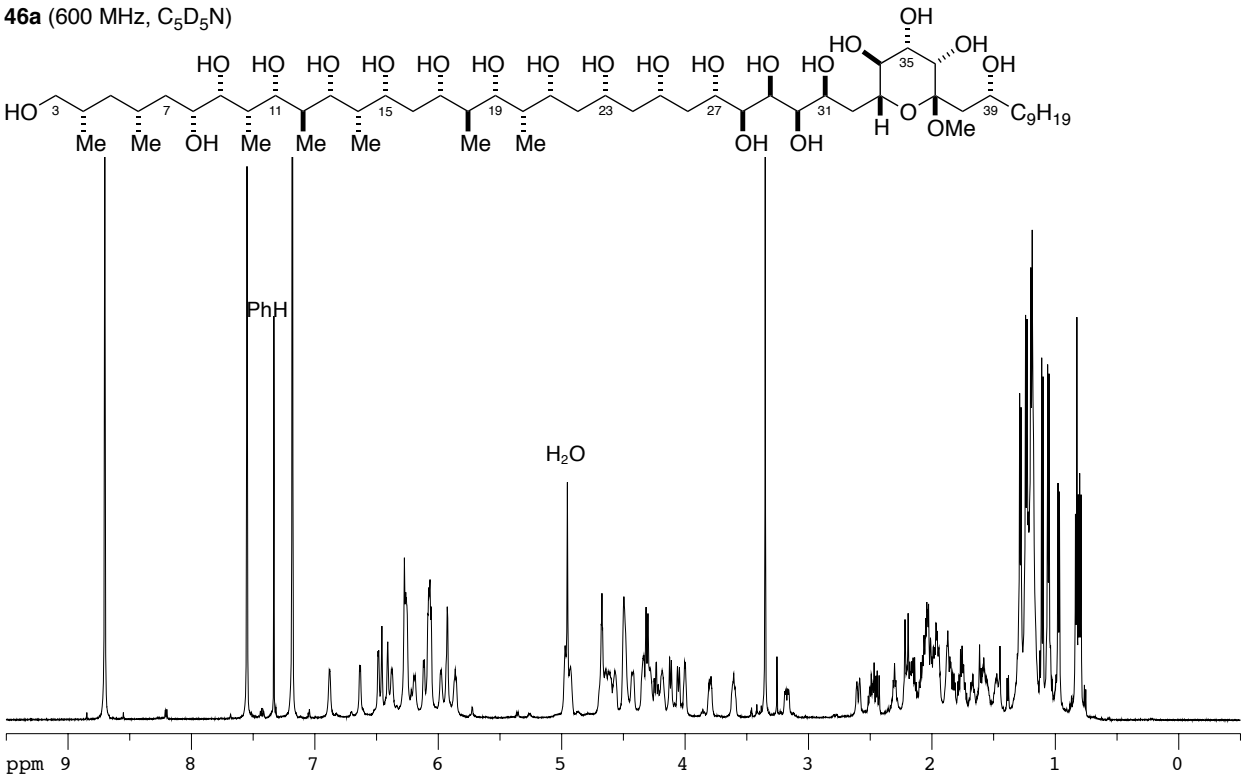


89 (125 MHz, CD_3OD)

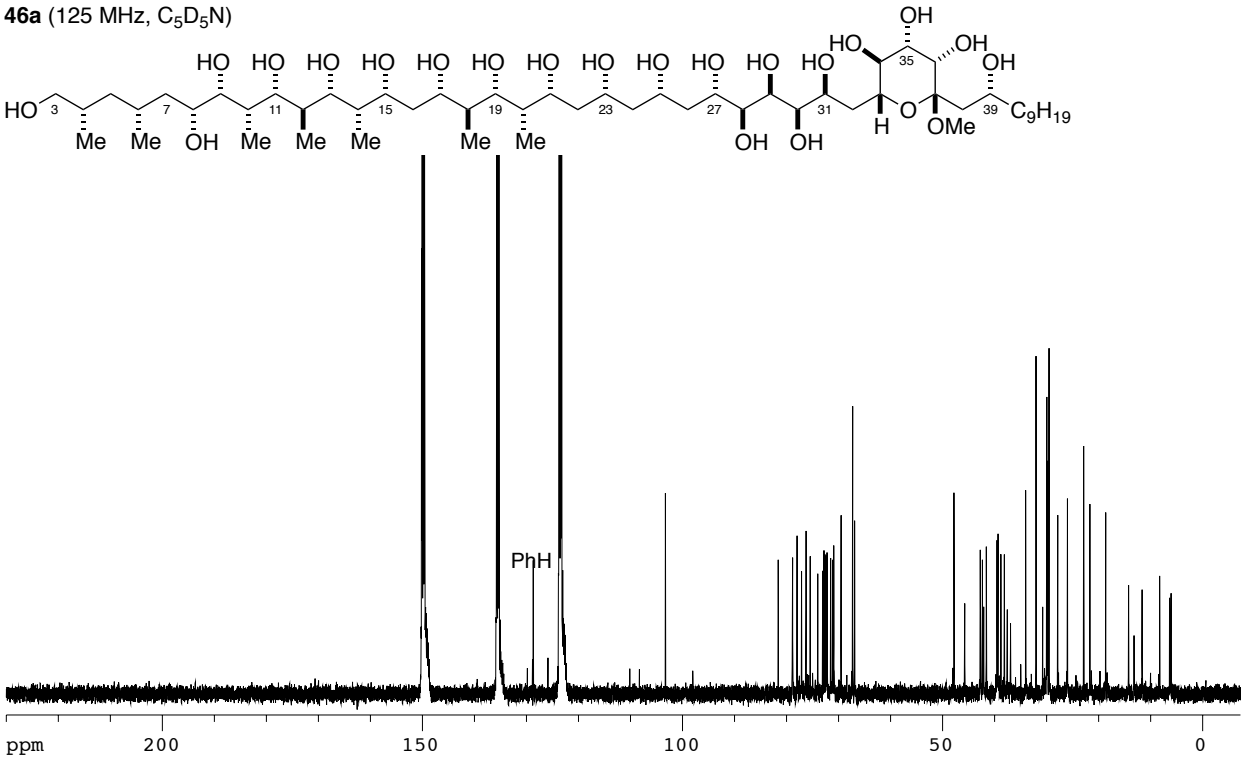


Compound 46a.

46a (600 MHz, C_5D_5N)

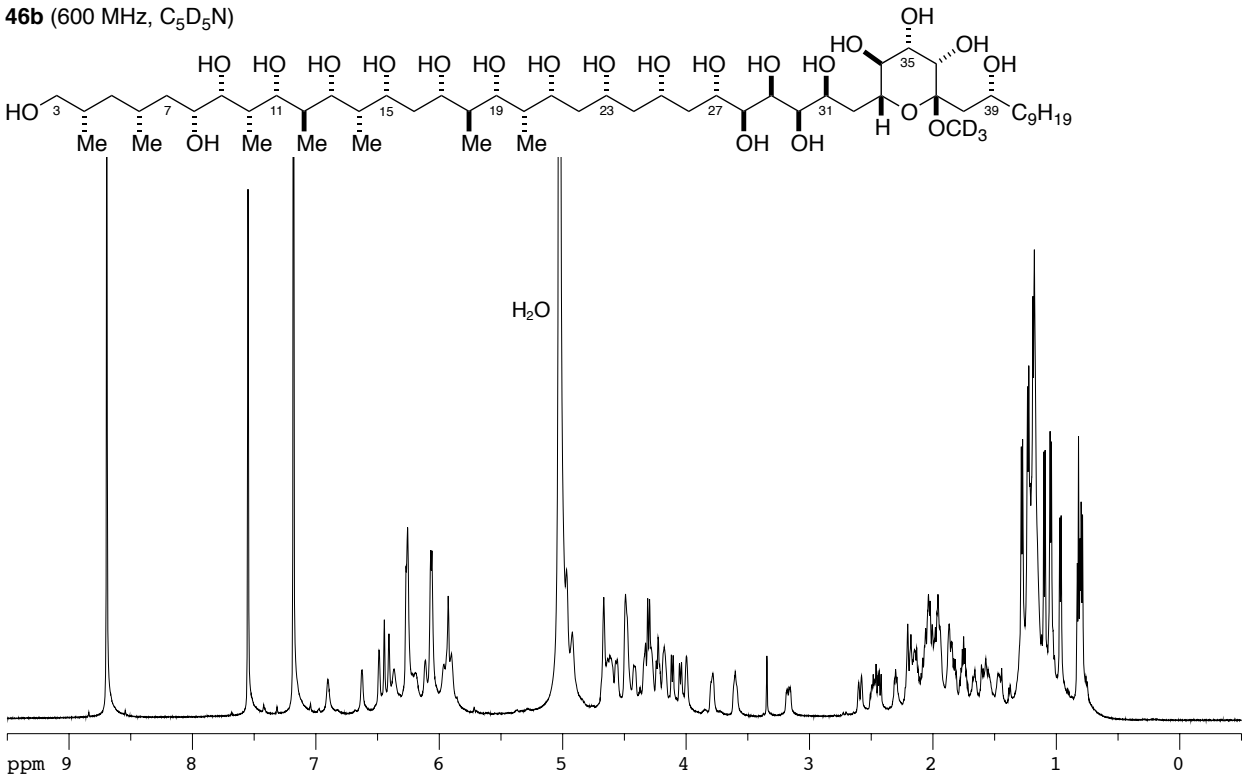


46a (125 MHz, C_5D_5N)

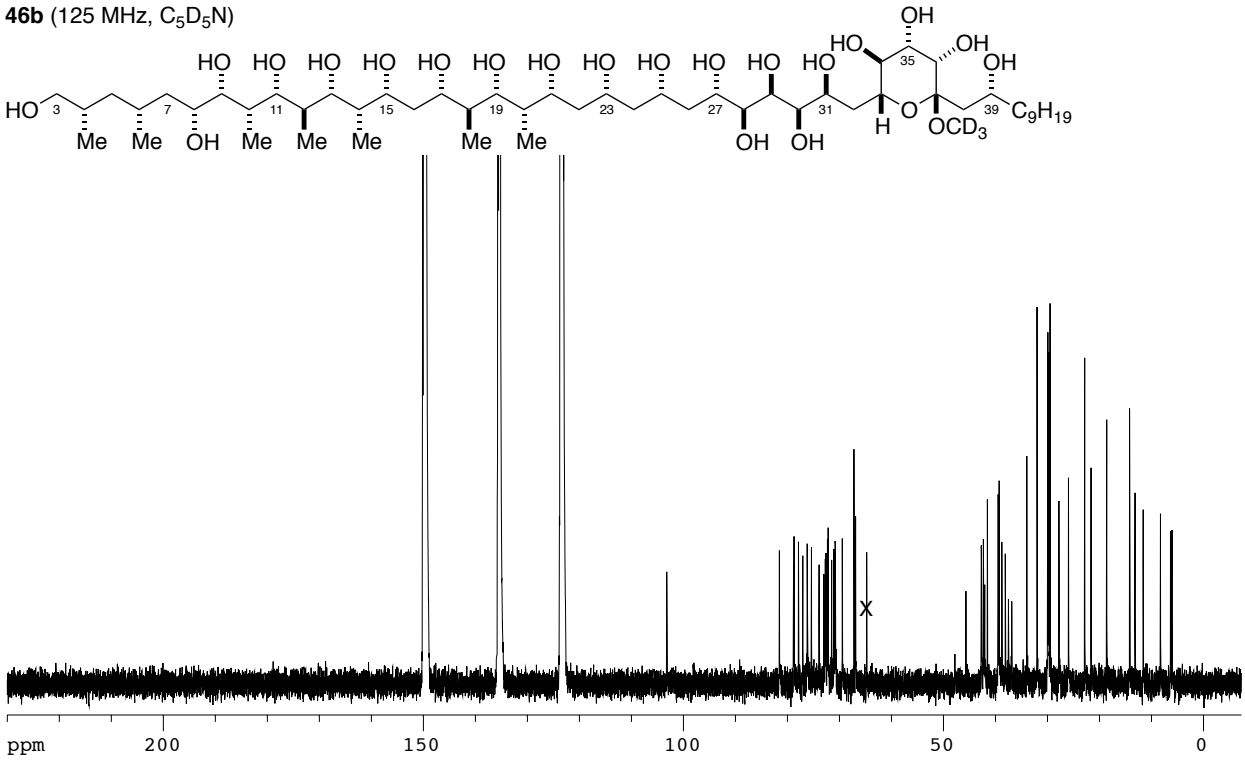


Compound 46b.

46b (600 MHz, C_5D_5N)

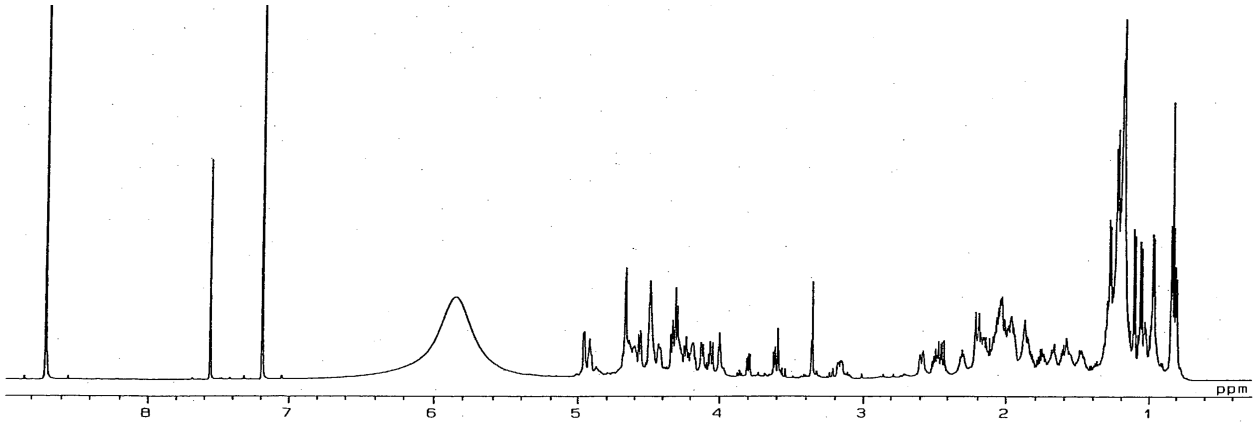


46b (125 MHz, C_5D_5N)

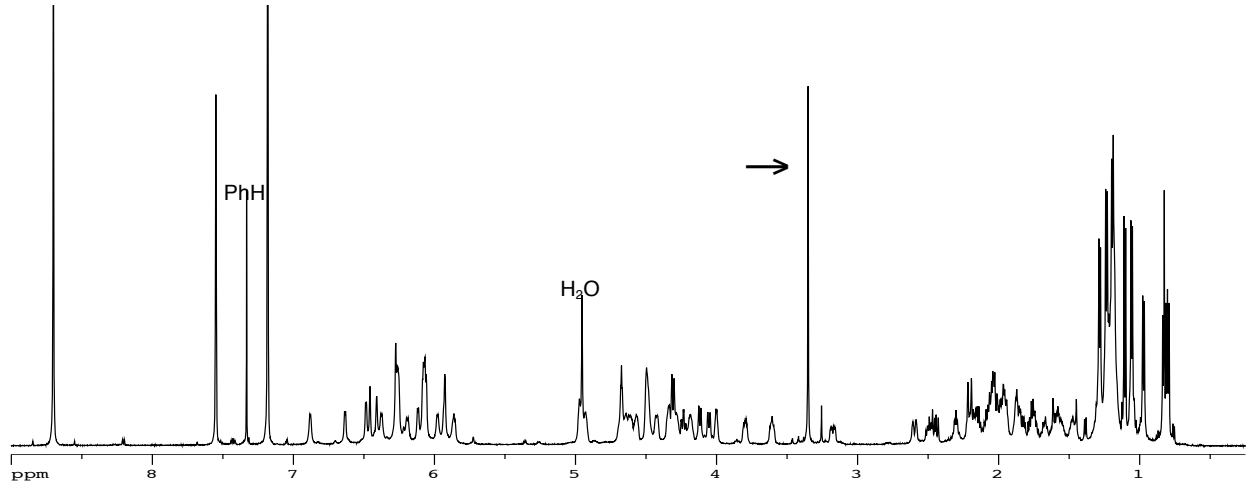


Comparison of the ^{1}H-NMR Spectrum Reported for 1[a] to Our Spectra for 46a[b] and 46b.

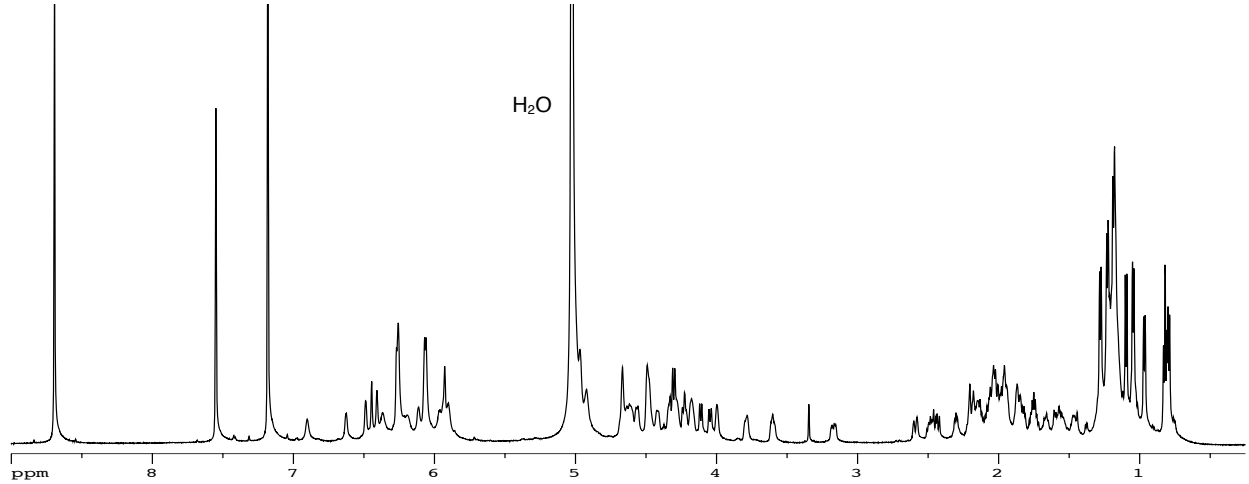
Sakuda "**1**" (600 MHz, C_5D_5N)



Evans **46a** (600 MHz, C_5D_5N)



Evans **46b** (600 MHz, C_5D_5N)

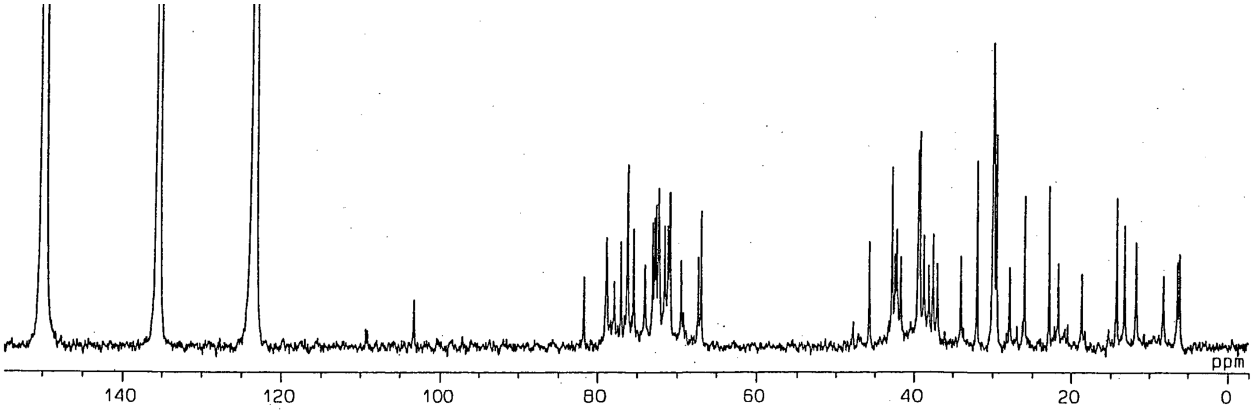


[a] Reproduced from: H. Ikeda, N. Matsumori, M. Ono, A. Suzuki, A. Isogai, H. Nagasawa, S. Sakuda, *J. Org. Chem.* **2000**, *65*, 438–444.

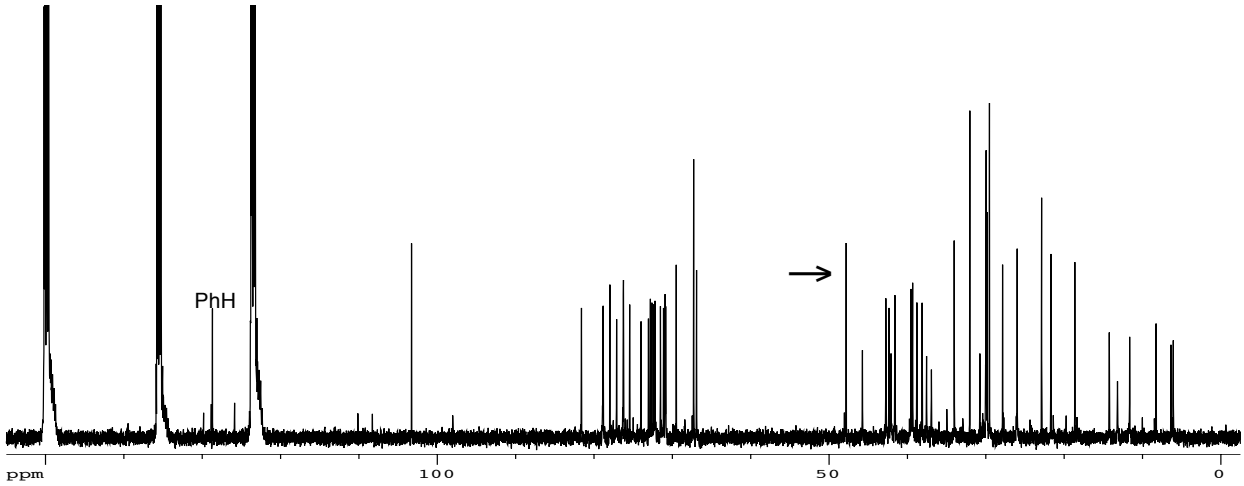
[b] Arrow (→) points at resonance corresponding to the methyl group (C_{56}-$\mathbf{H_3}$) of lactol methyl ether **46a**.

Comparison of the ^{13}C-NMR Spectrum Reported for 1[a] to Our Spectra for 46a[b] and 46b.

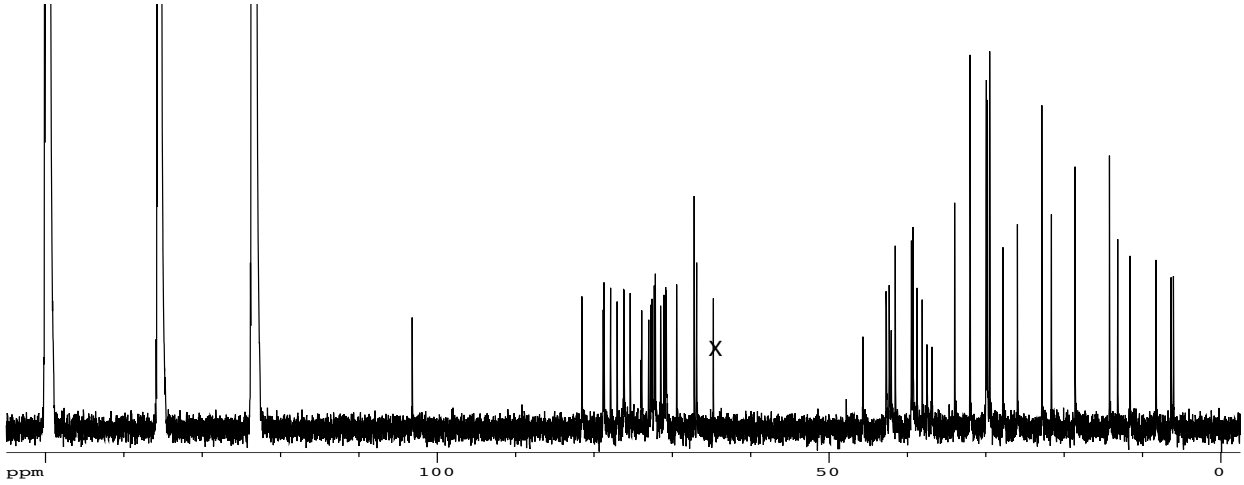
Sakuda "**1**" (150 MHz, C_5D_5N)



Evans **46a** (125 MHz, C_5D_5N)



Evans **46b** (125 MHz, C_5D_5N)

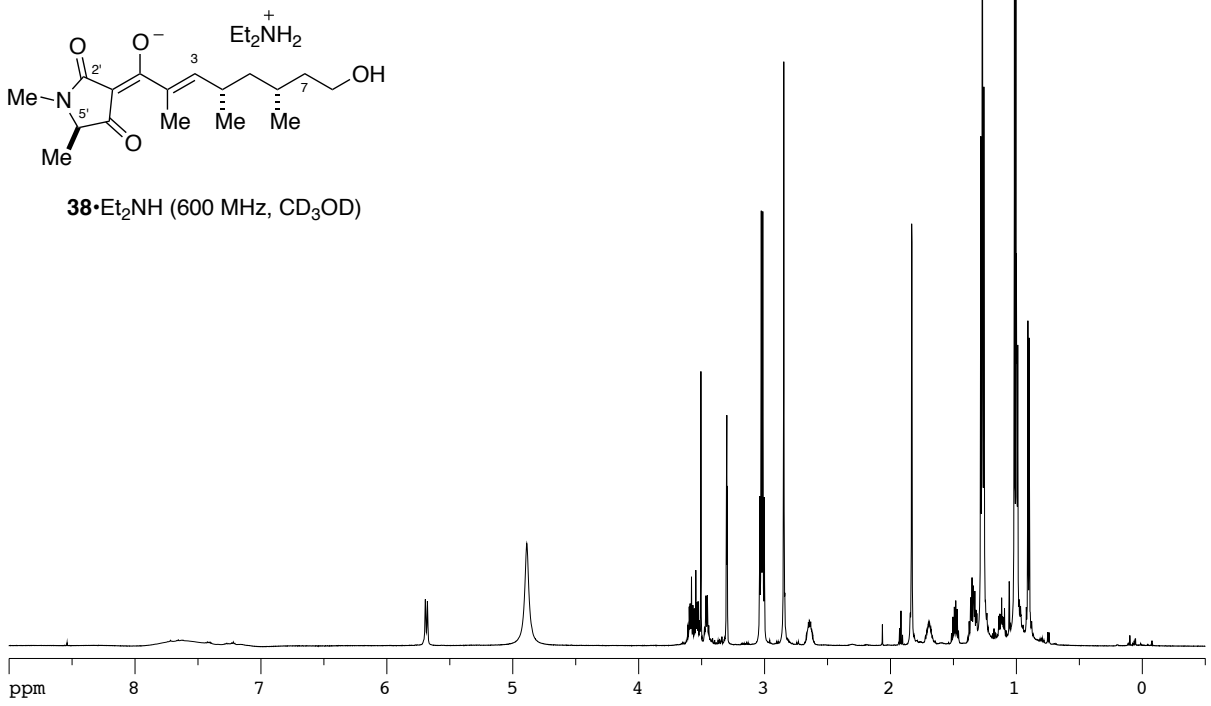


[a] Reproduced from: H. Ikeda, N. Matsumori, M. Ono, A. Suzuki, A. Isogai, H. Nagasawa, S. Sakuda, *J. Org. Chem.* **2000**, *65*, 438–444.

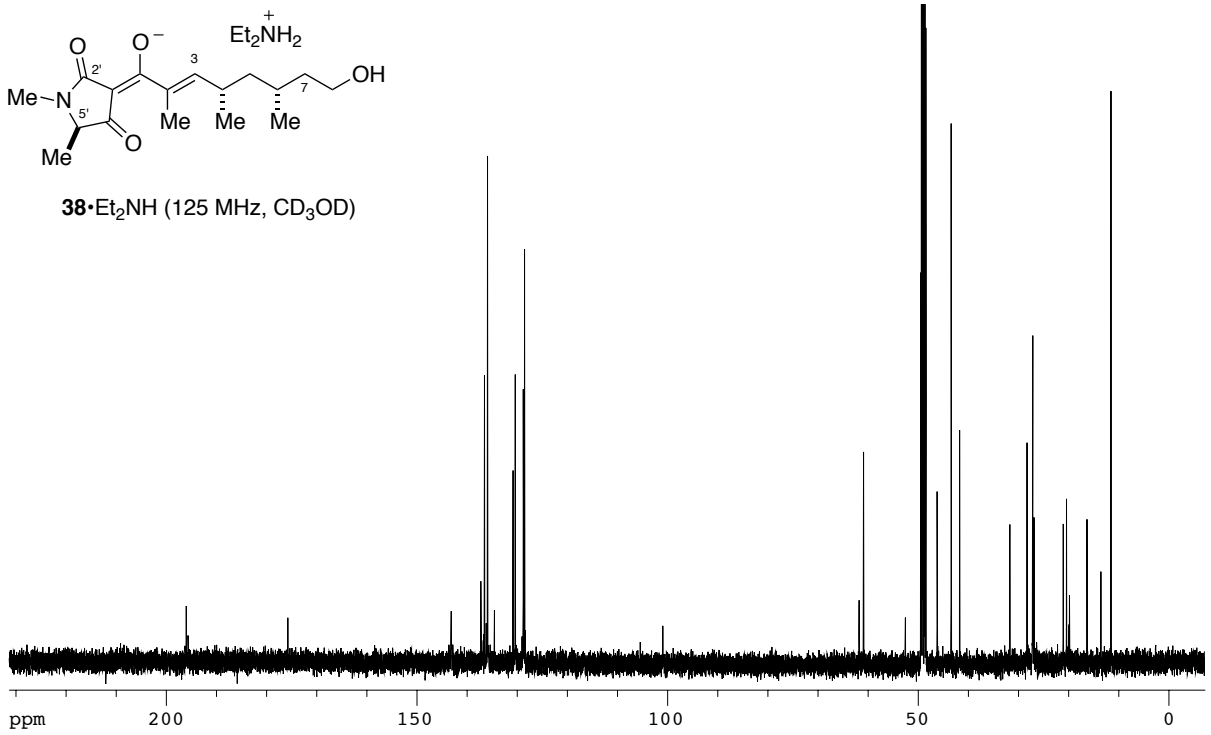
[b] Arrow (→) points at resonance corresponding to the methyl group (C-56) of lactol methyl ether **46a**.

Chapter 4

Compound 38•Et_2NH.

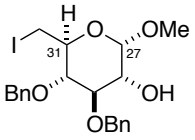


38•Et_2NH (600 MHz, CD_3OD)

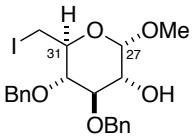


38•Et_2NH (125 MHz, CD_3OD)

Compound 127.

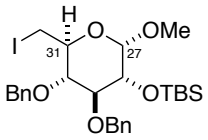


127 (600 MHz, $CDCl_3$)

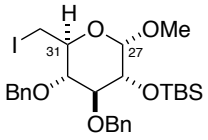


127 (125 MHz, $CDCl_3$)

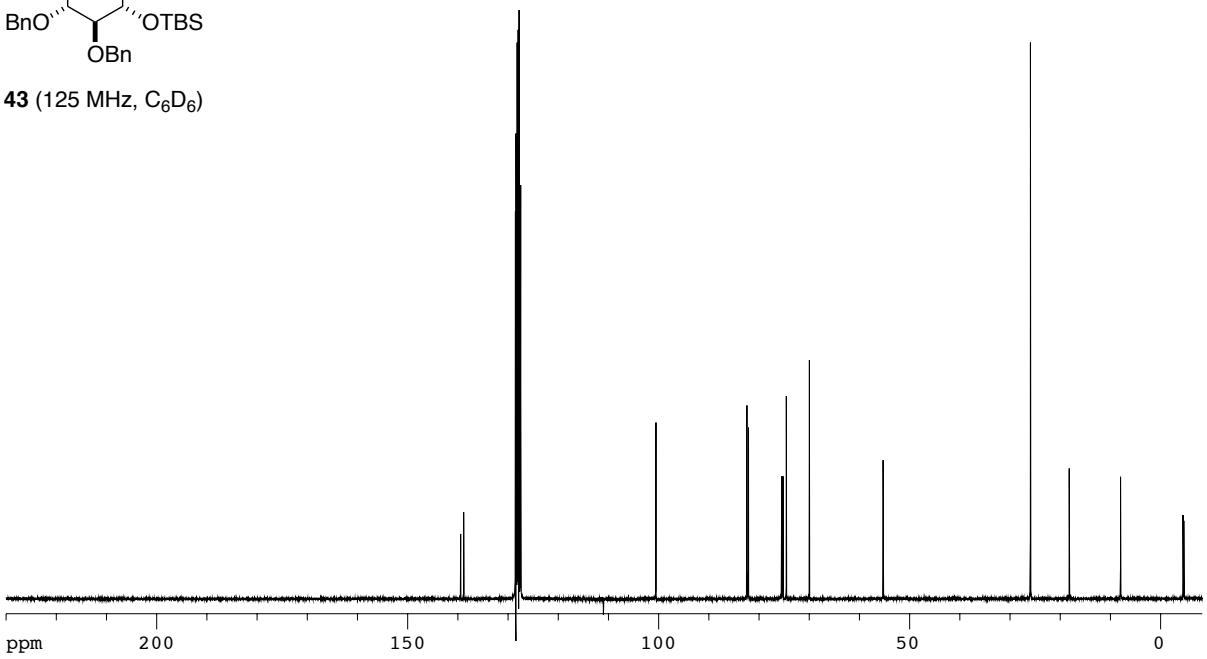
Compound 43.



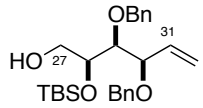
43 (600 MHz, C_6D_6)



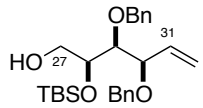
43 (125 MHz, C_6D_6)



Compound 44.

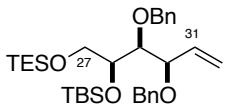


44 (600 MHz, $CDCl_3$)

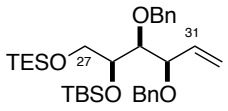


44 (125 MHz, $CDCl_3$)

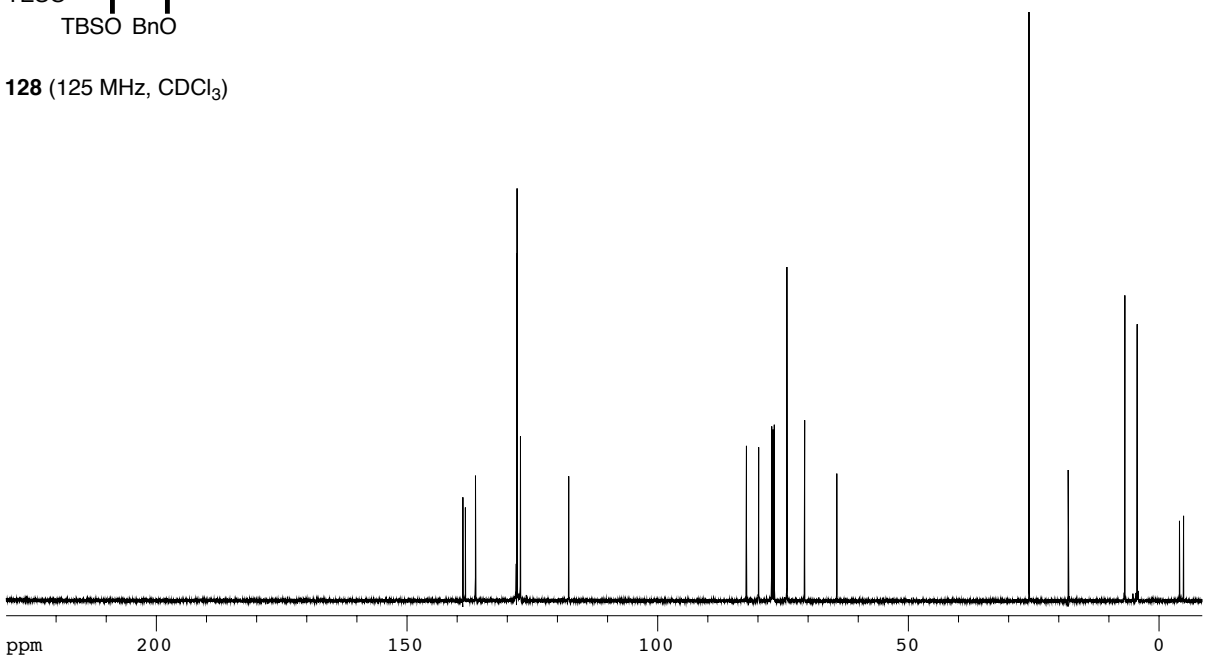
Compound 128.



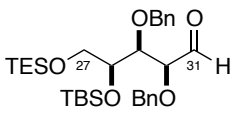
128 (600 MHz, $CDCl_3$)



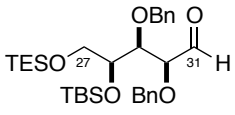
128 (125 MHz, $CDCl_3$)



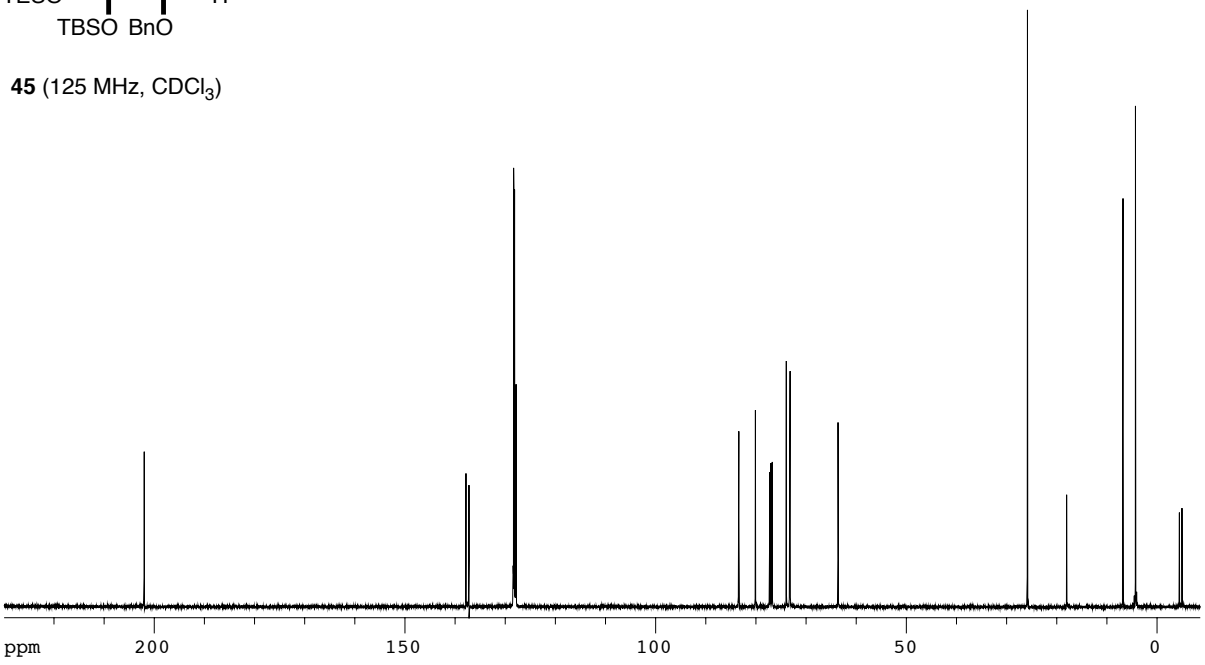
Compound 45.



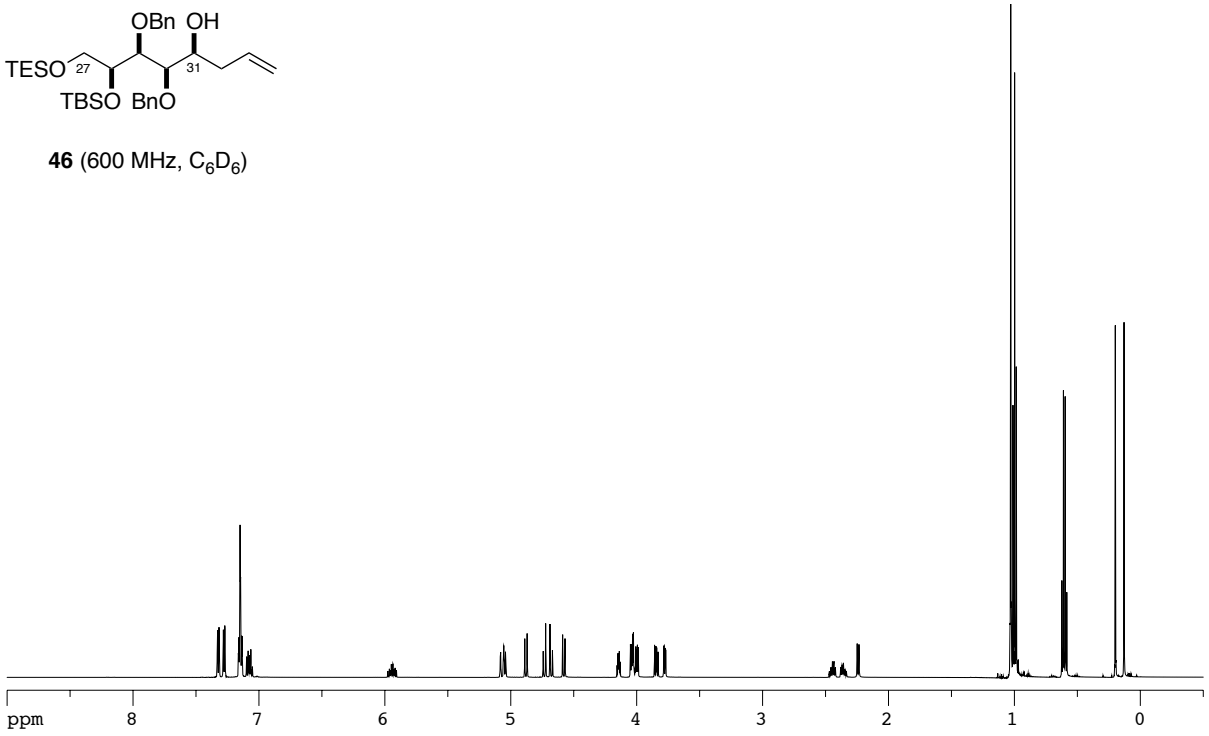
45 (600 MHz, $CDCl_3$)



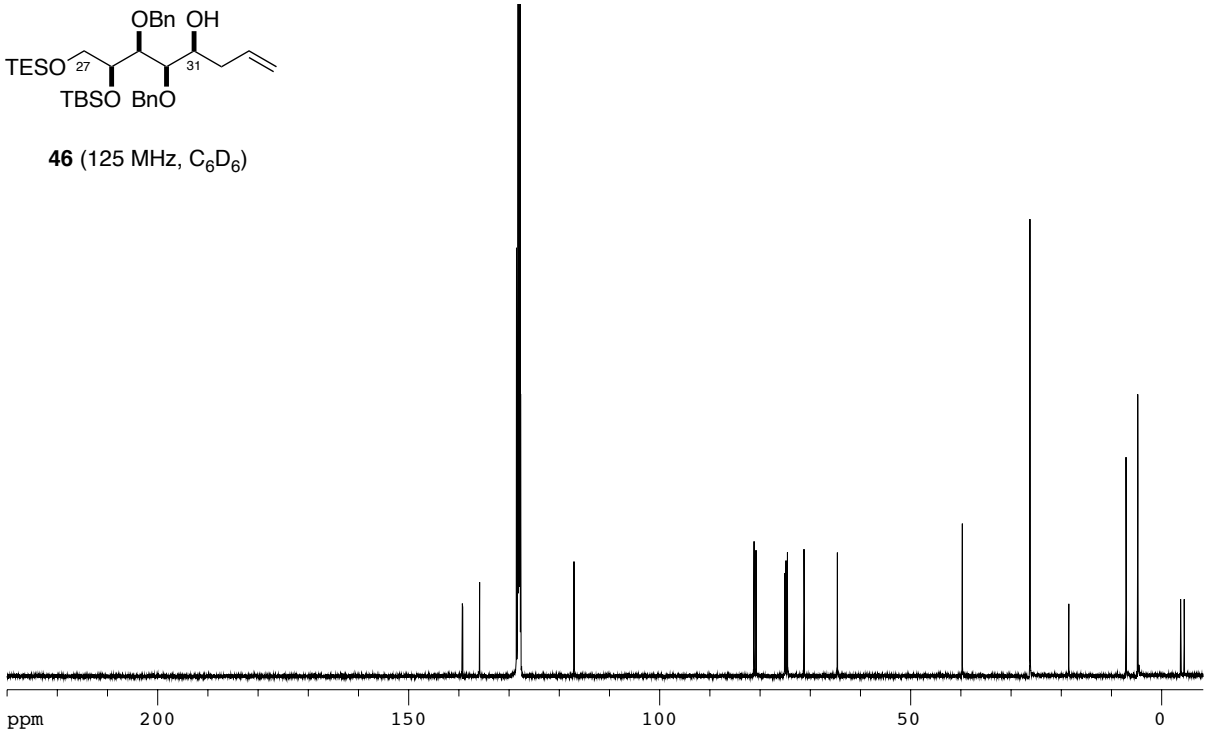
45 (125 MHz, $CDCl_3$)



Compound 46.

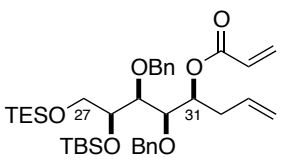


46 (600 MHz, C_6D_6)

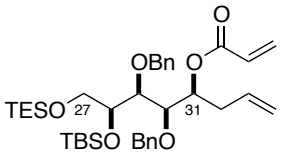


46 (125 MHz, C_6D_6)

Compound 132.

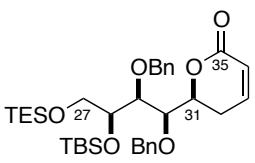


132 (600 MHz, $CDCl_3$)

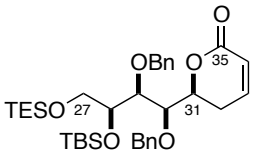


132 (125 MHz, $CDCl_3$)

Compound 47.

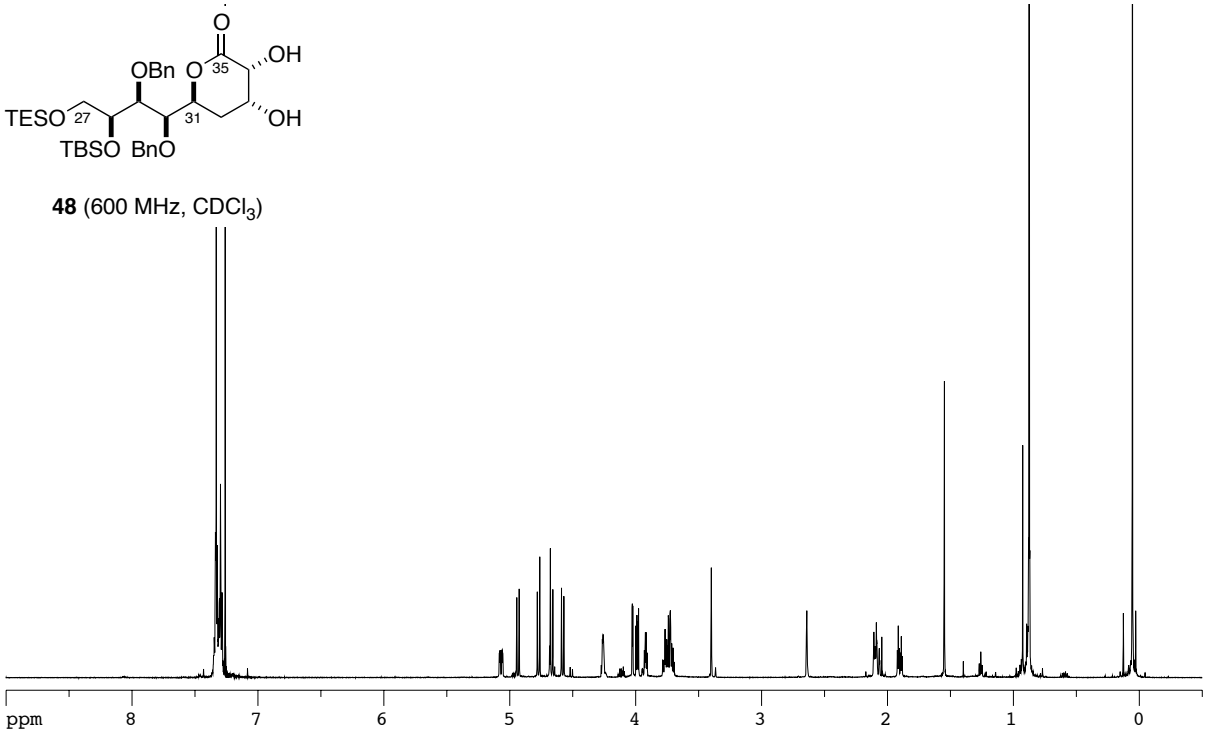


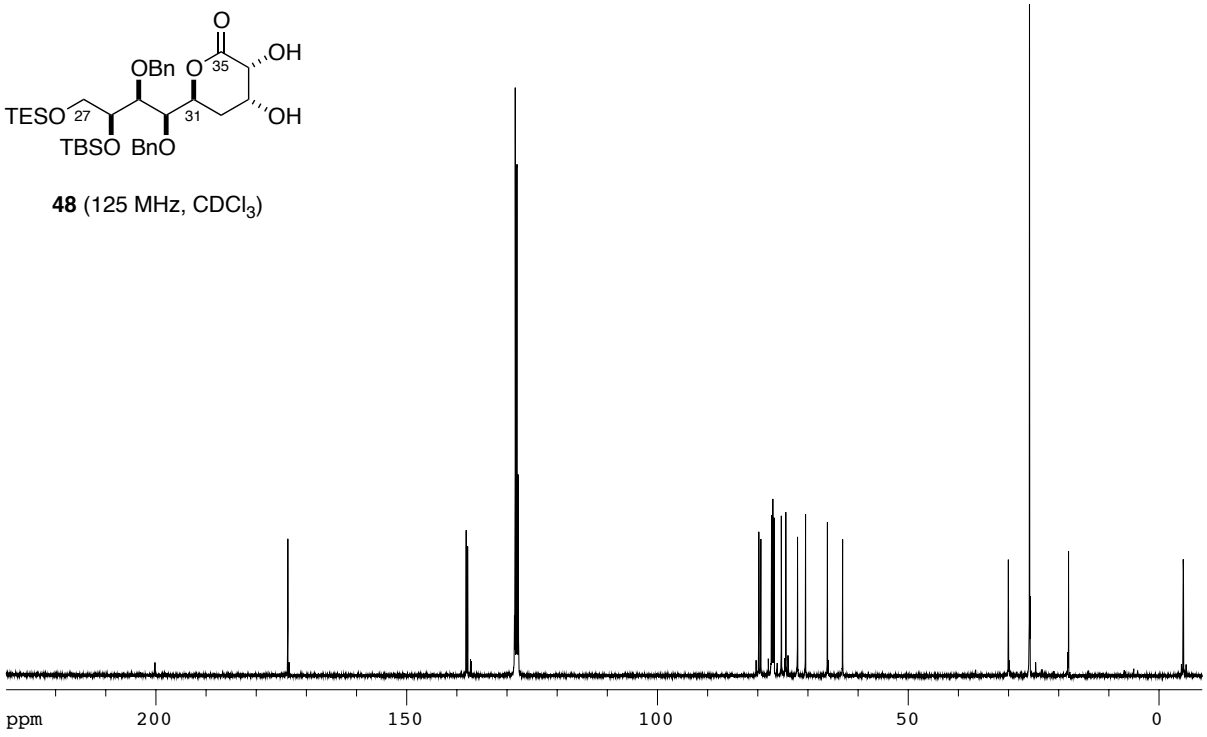
47 (600 MHz, $CDCl_3$)



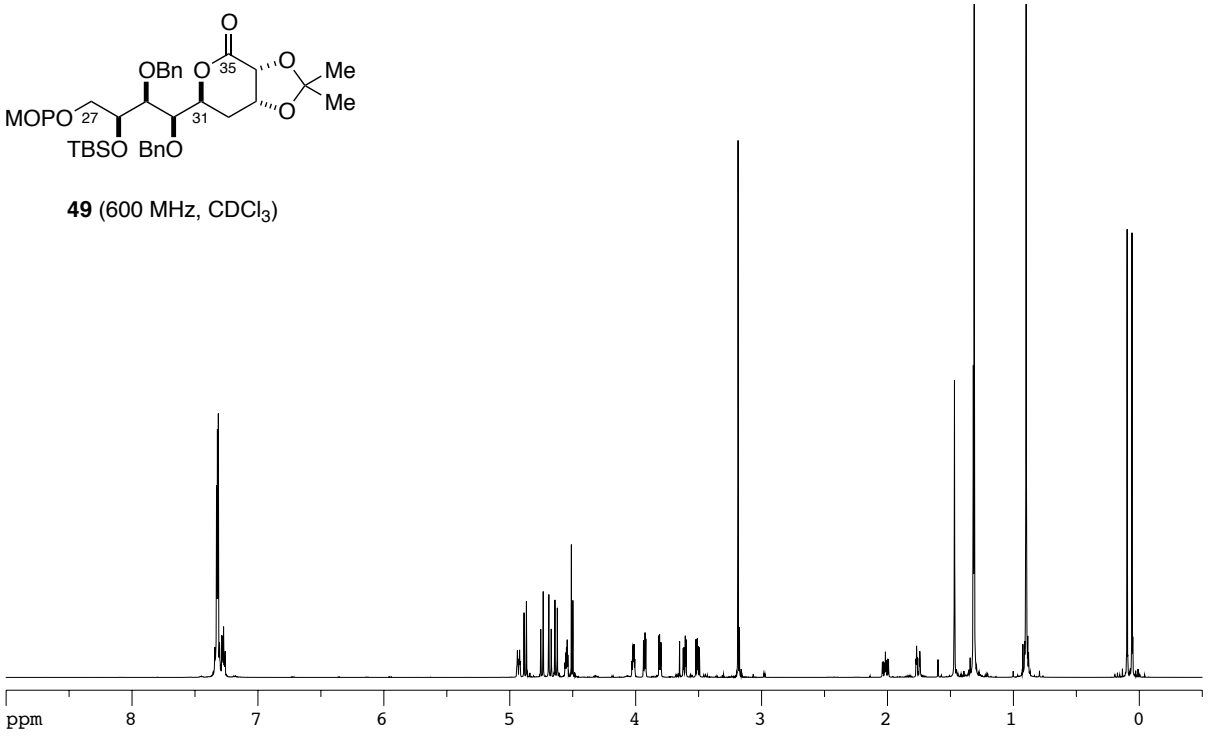
47 (125 MHz, $CDCl_3$)

Compound 48.

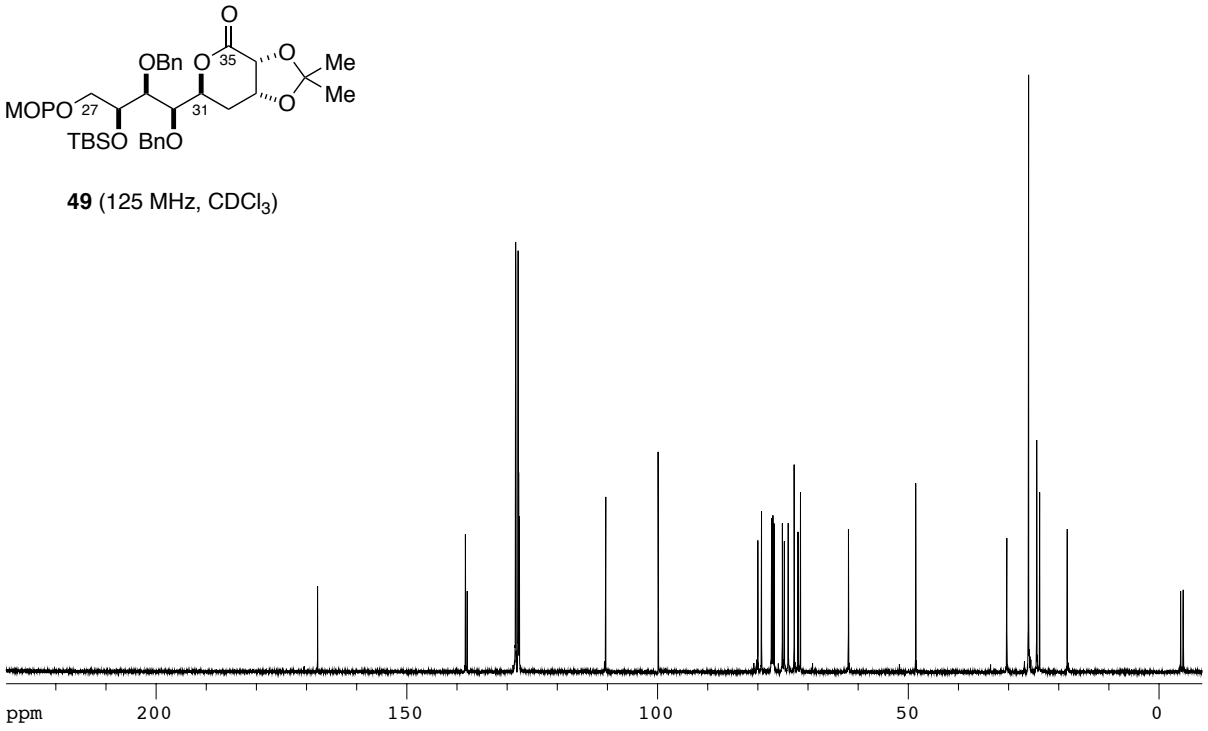

O
OBn
O
35
OH
TESO
27
31
OH
TBSO
BnO
48 (600 MHz, CDCl3)
ppm
8
7
6
5
4
3
2
1
0


O
OBn
O
35
OH
TESO
27
31
OH
TBSO
BnO
48 (125 MHz, CDCl3)
ppm
200
150
100
50
0

Compound 49.

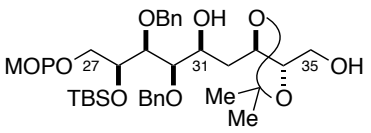


49 (600 MHz, $CDCl_3$)

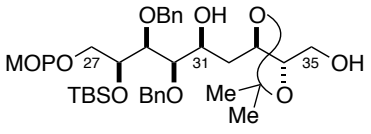


49 (125 MHz, $CDCl_3$)

Compound 50.

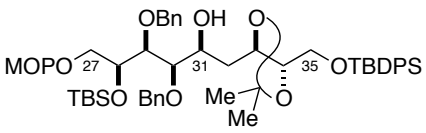


50 (600 MHz, $CDCl_3$)

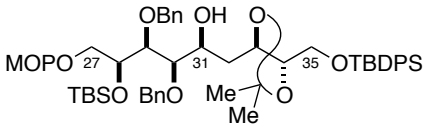


50 (125 MHz, $CDCl_3$)

Compound 133.

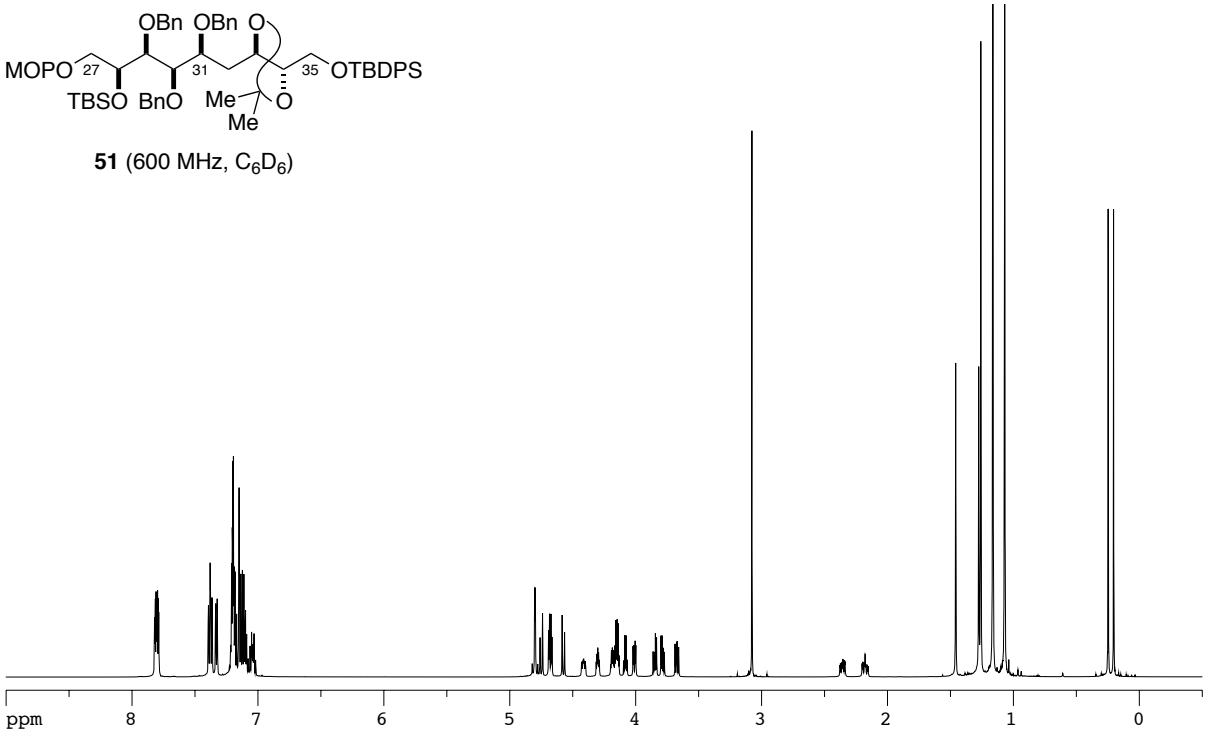


133 (600 MHz, C_6D_6)

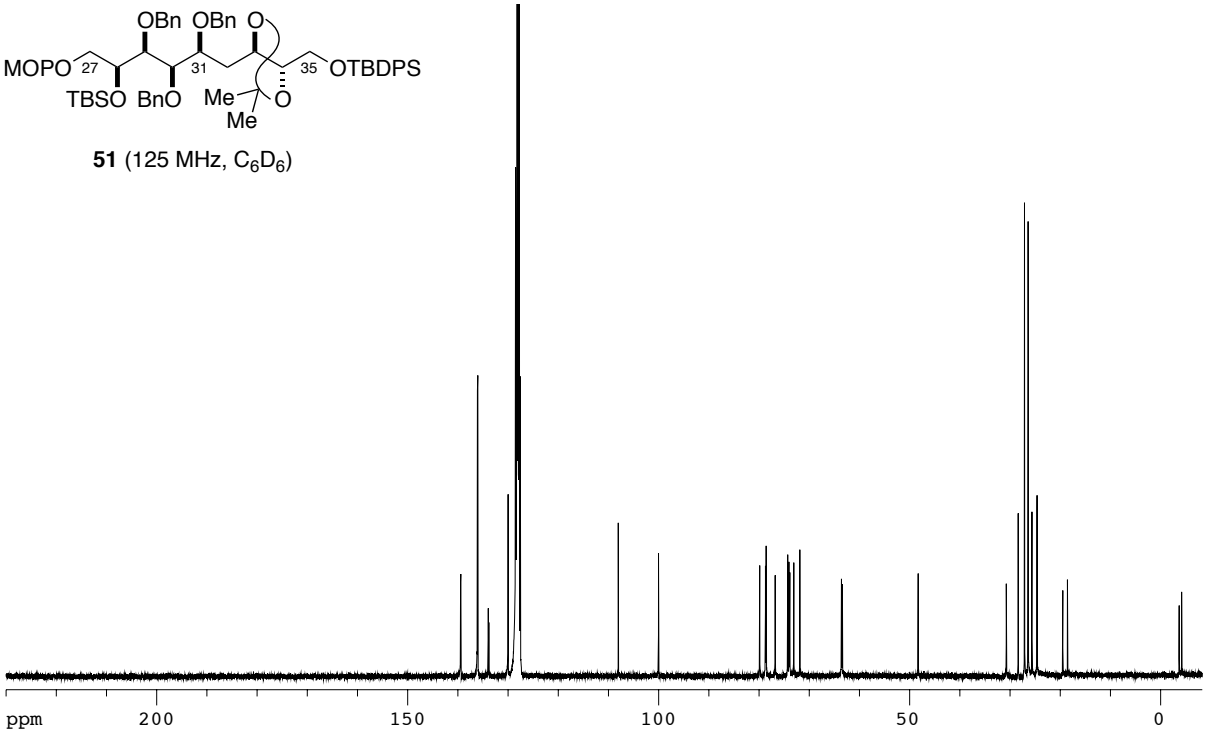


133 (125 MHz, C_6D_6)

Compound 51.

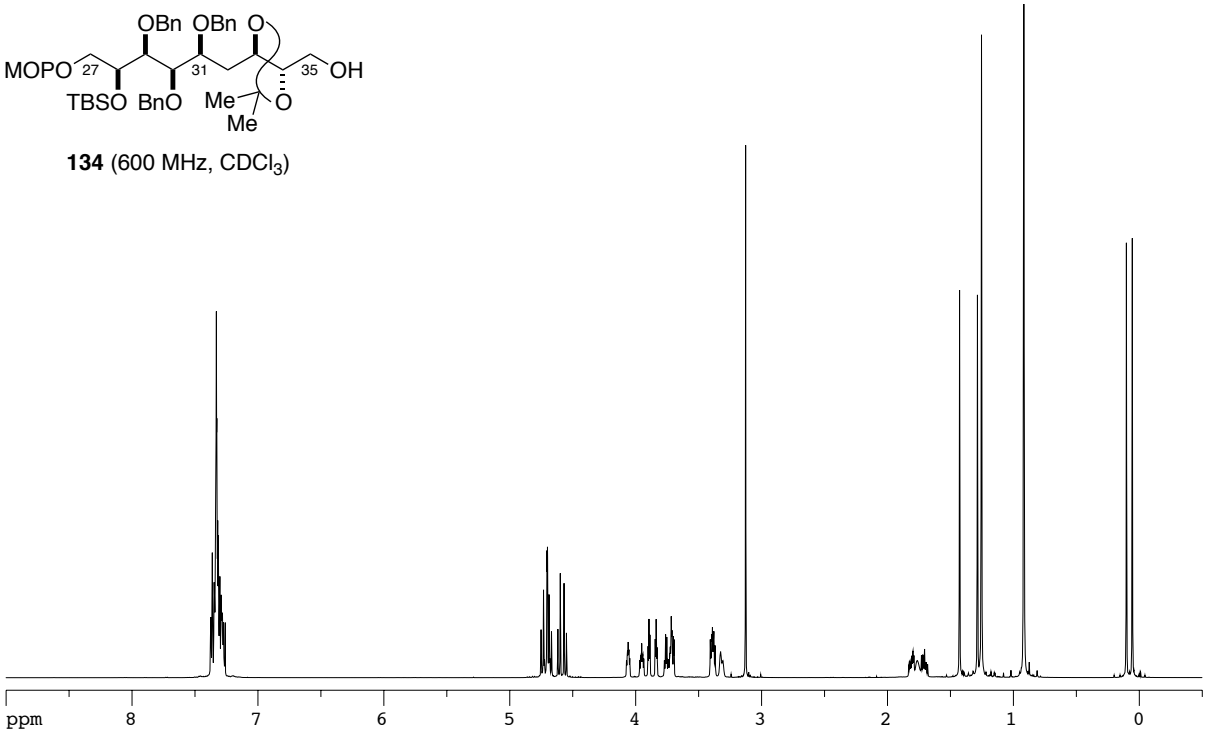


51 (600 MHz, C_6D_6)

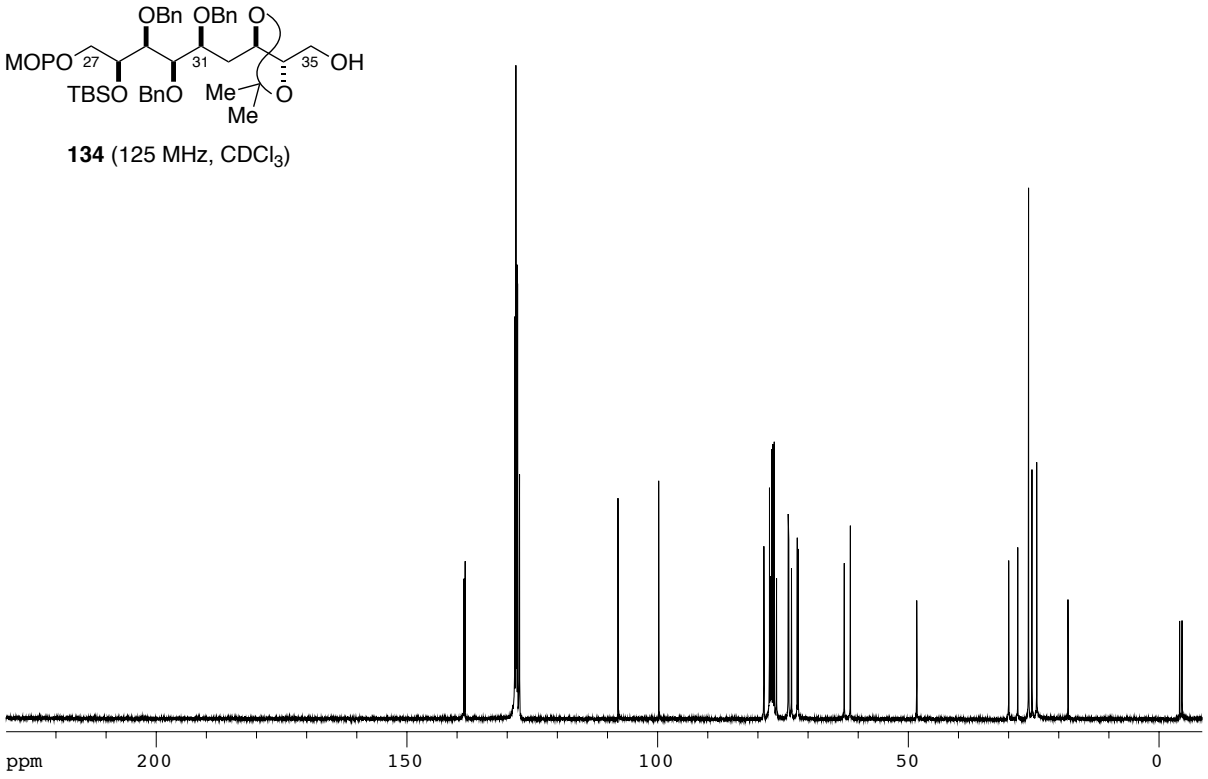


51 (125 MHz, C_6D_6)

Compound 134.

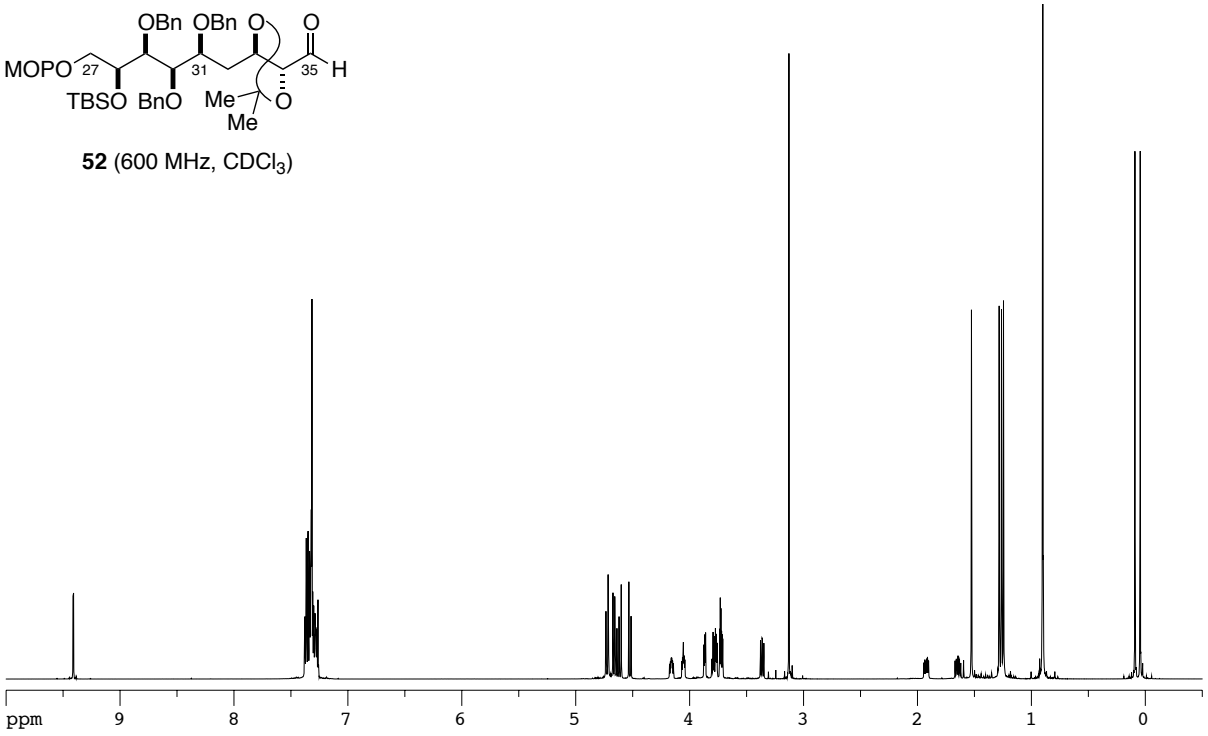


134 (600 MHz, $CDCl_3$)

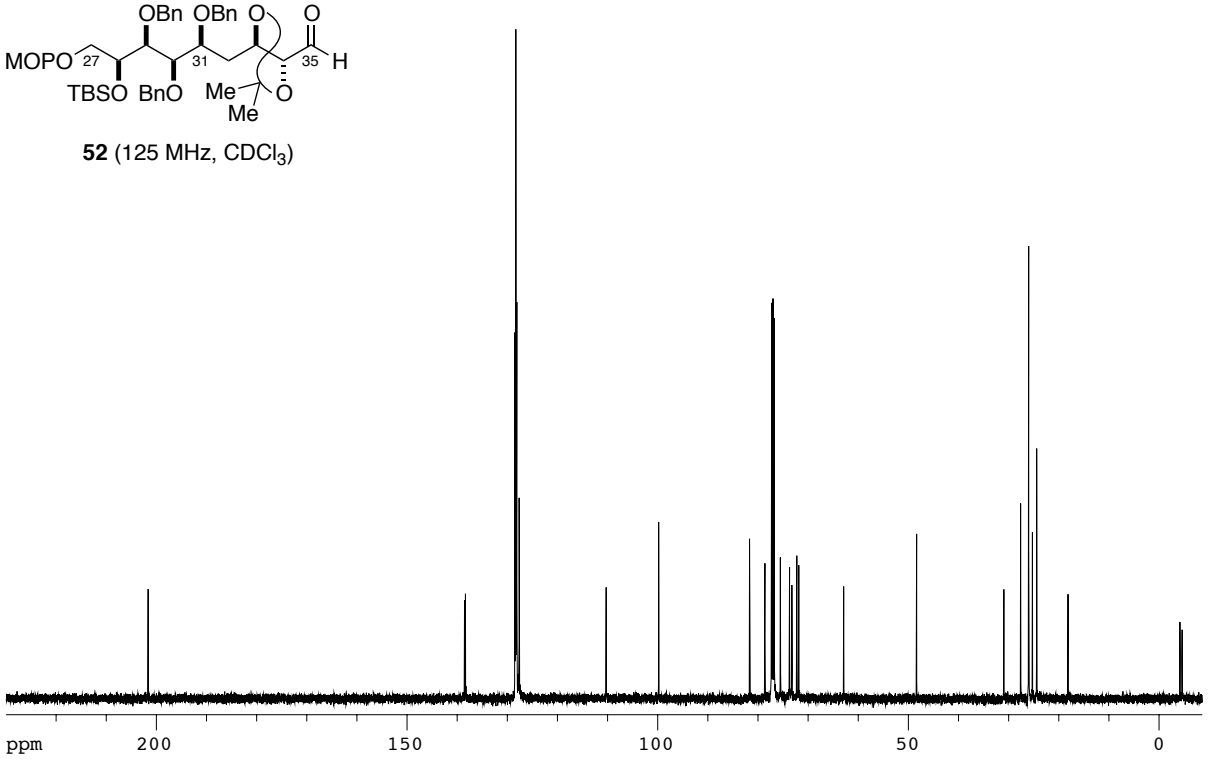


134 (125 MHz, $CDCl_3$)

Compound 52.

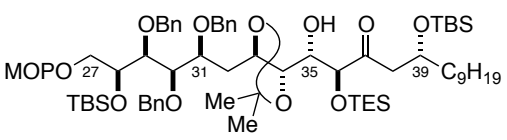


52 (600 MHz, $CDCl_3$)

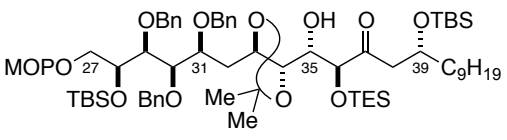


52 (125 MHz, $CDCl_3$)

Compound 54.

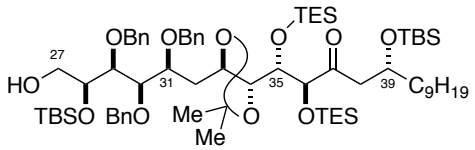


54 (600 MHz, C_6D_6)

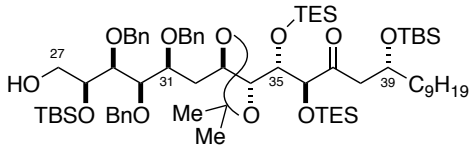


54 (125 MHz, C_6D_6)

Compound 135.

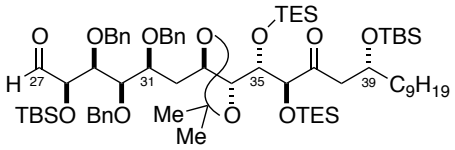


135 (600 MHz, $CDCl_3$)

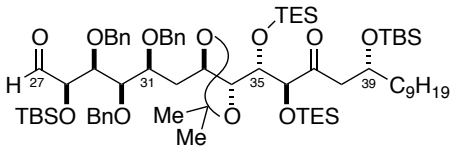


135 (125 MHz, $CDCl_3$)

Compound 41.



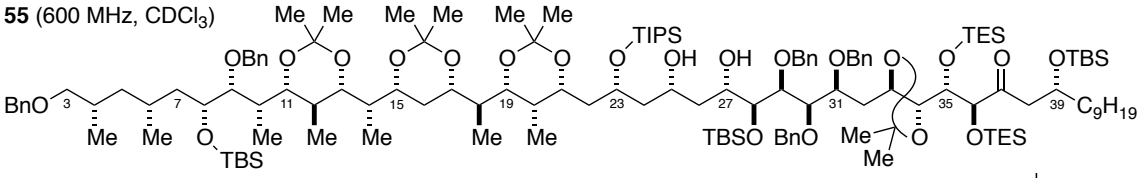
41 (600 MHz, $CDCl_3$)

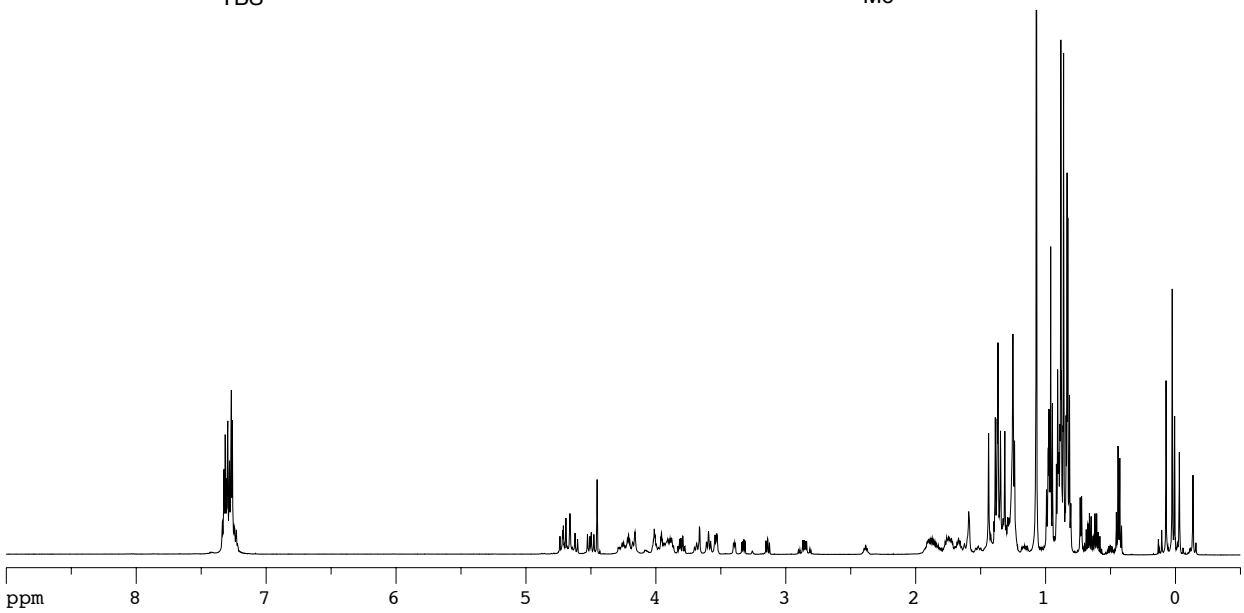


41 (125 MHz, $CDCl_3$)

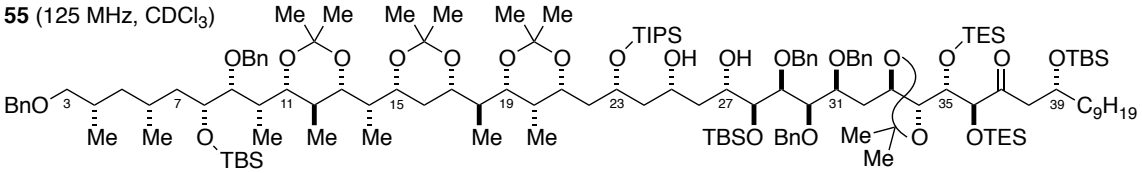
Compound 55.

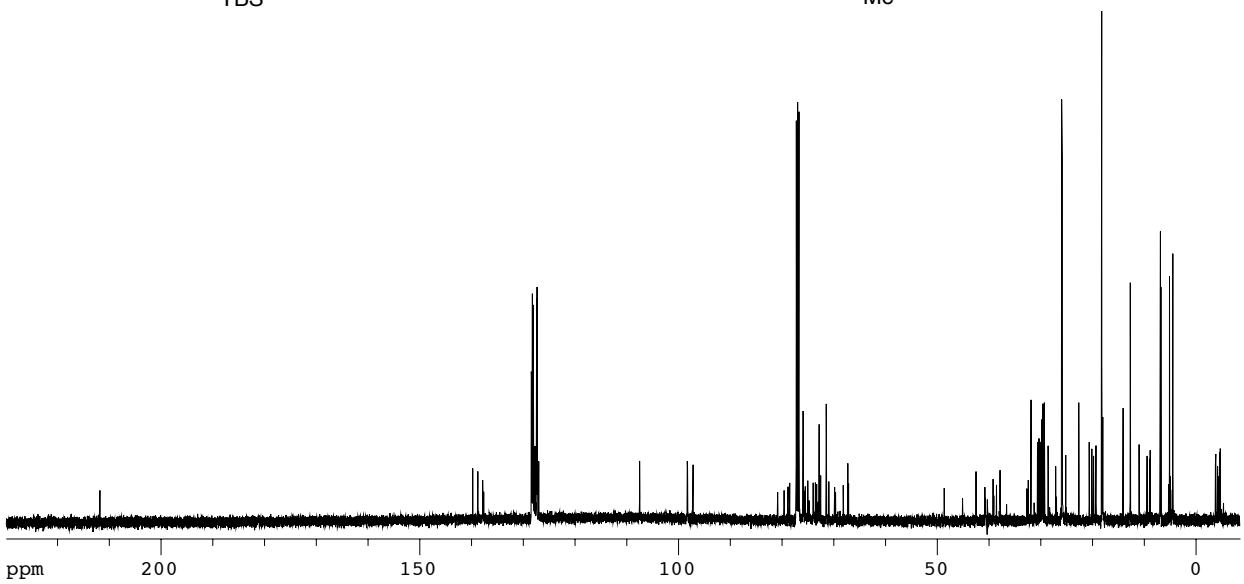
55 (600 MHz, $CDCl_3$)





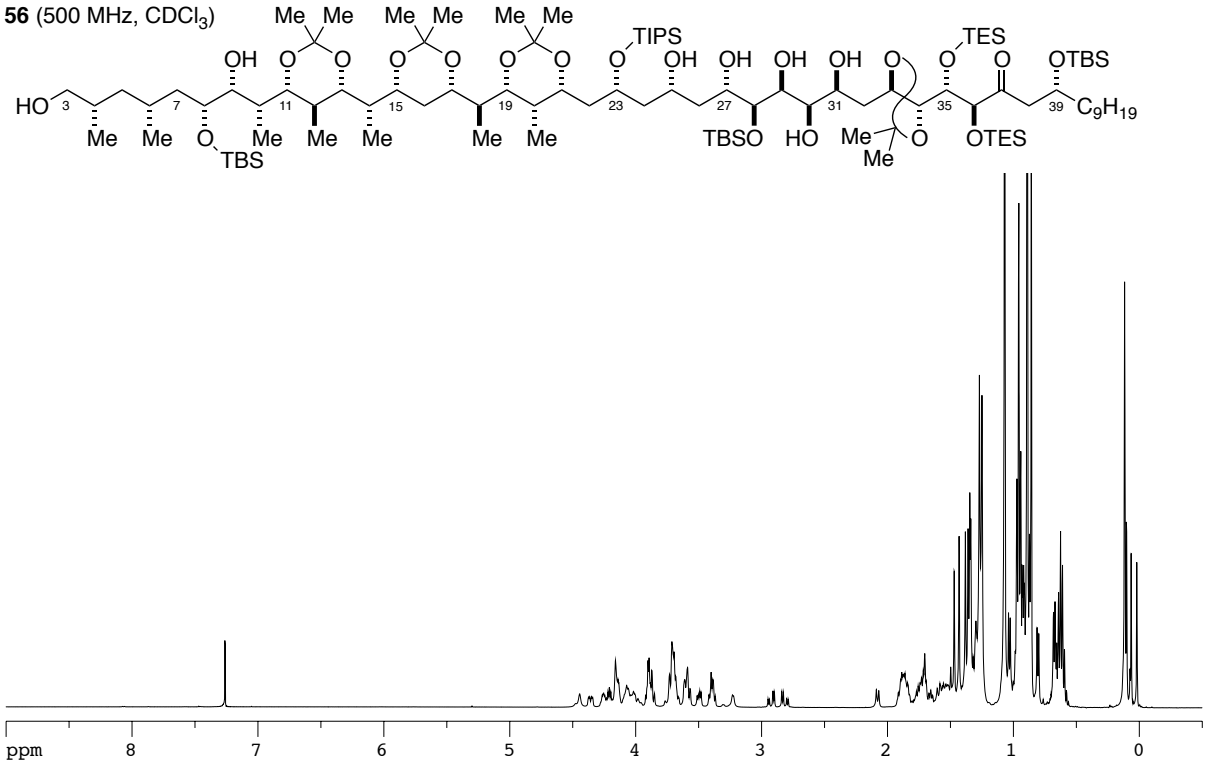
55 (125 MHz, $CDCl_3$)



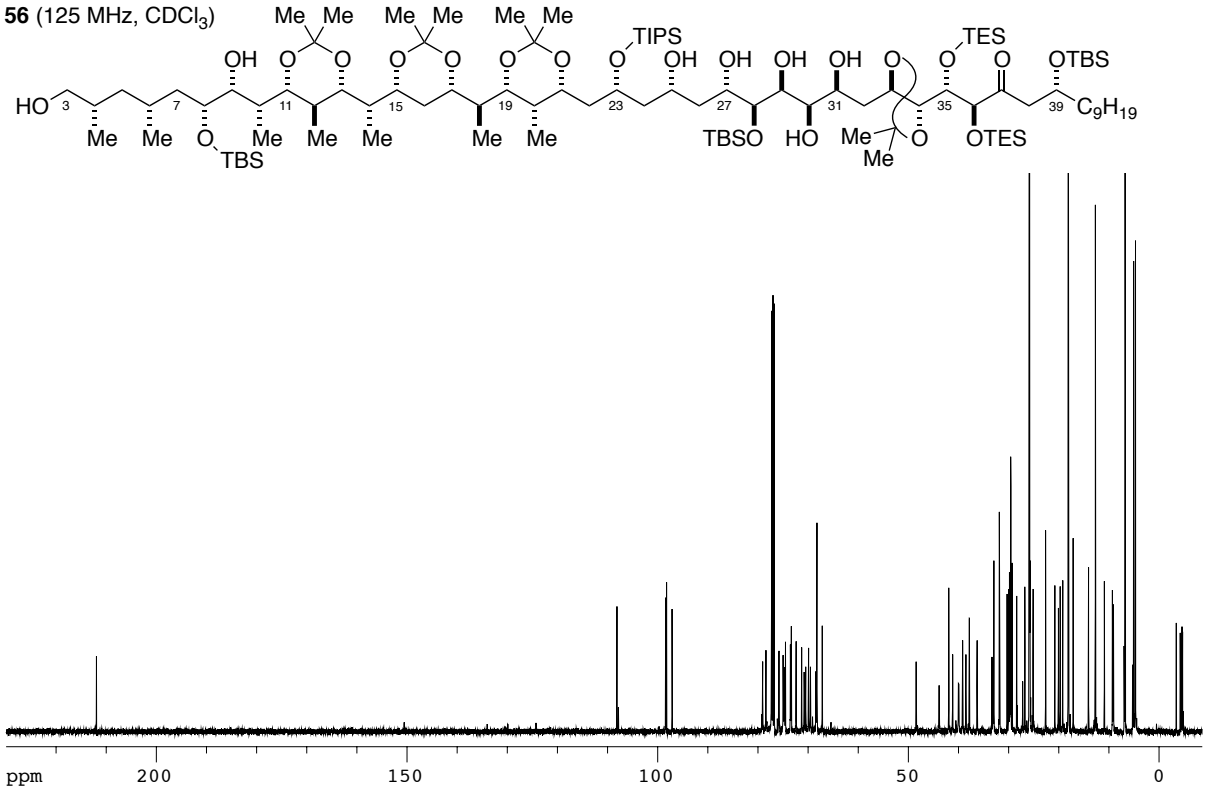


Compound 56.

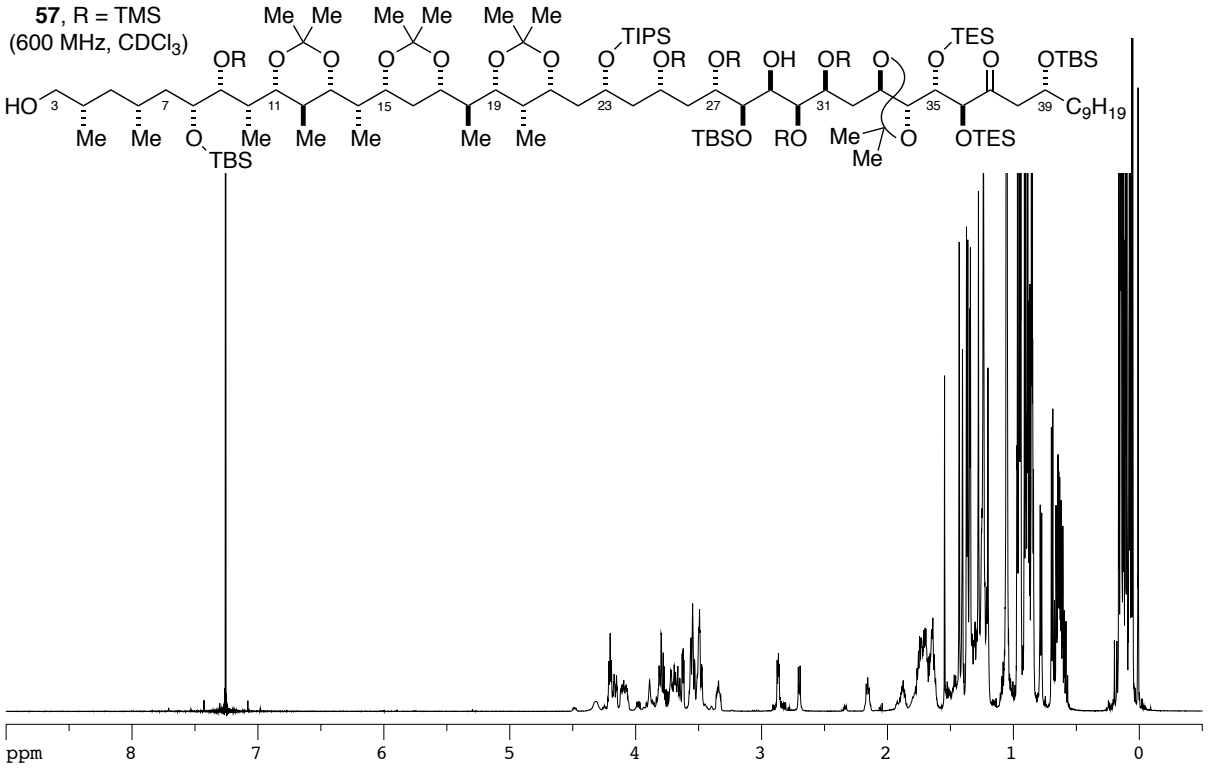
56 (500 MHz, $CDCl_3$)

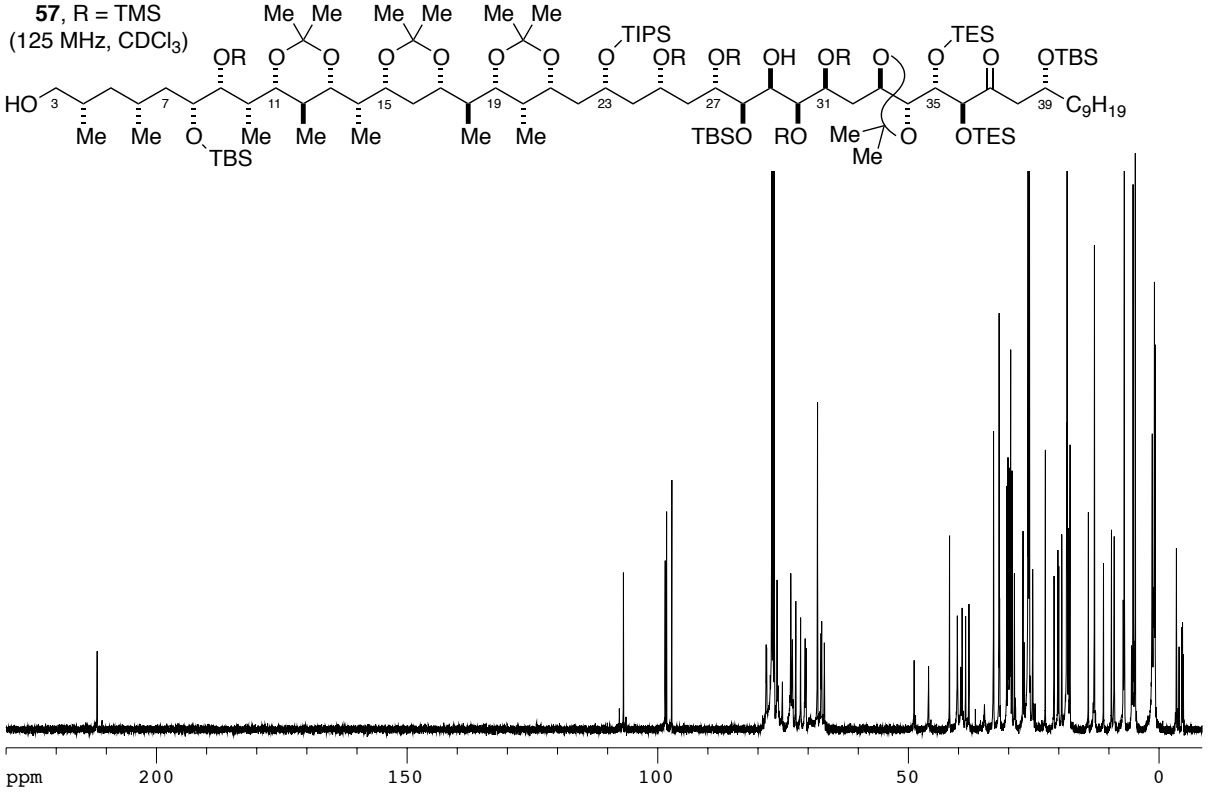


56 (125 MHz, $CDCl_3$)

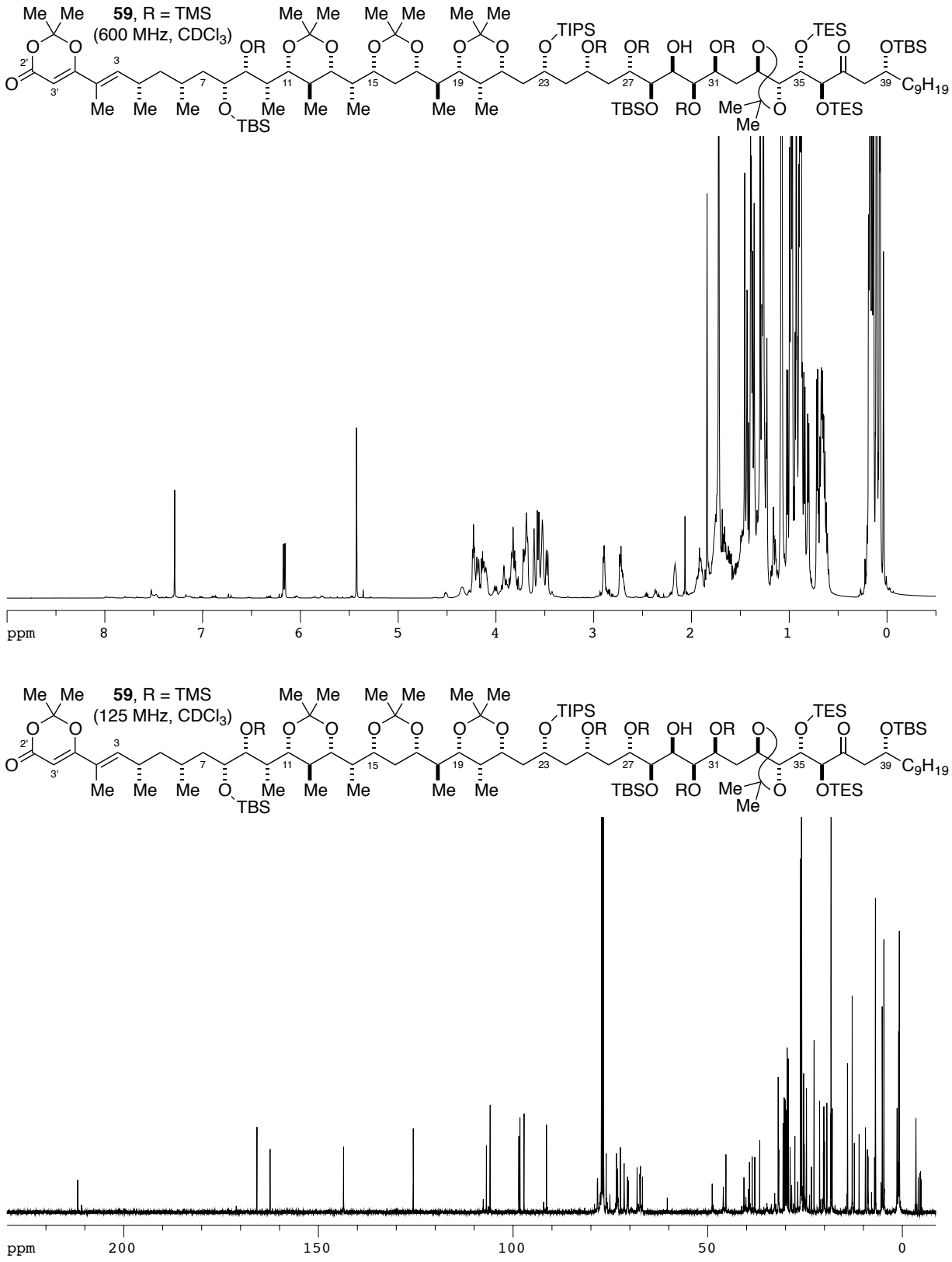


Compound 57.



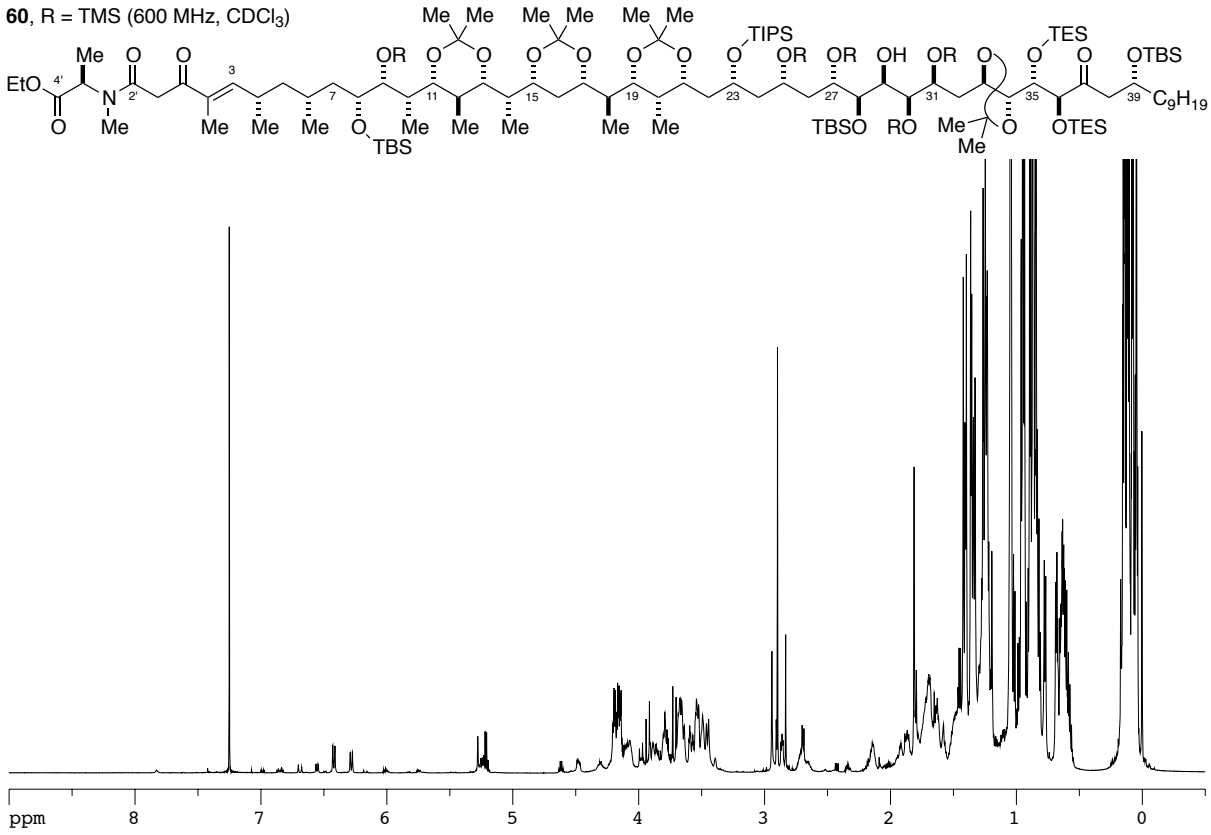


Compound 59.

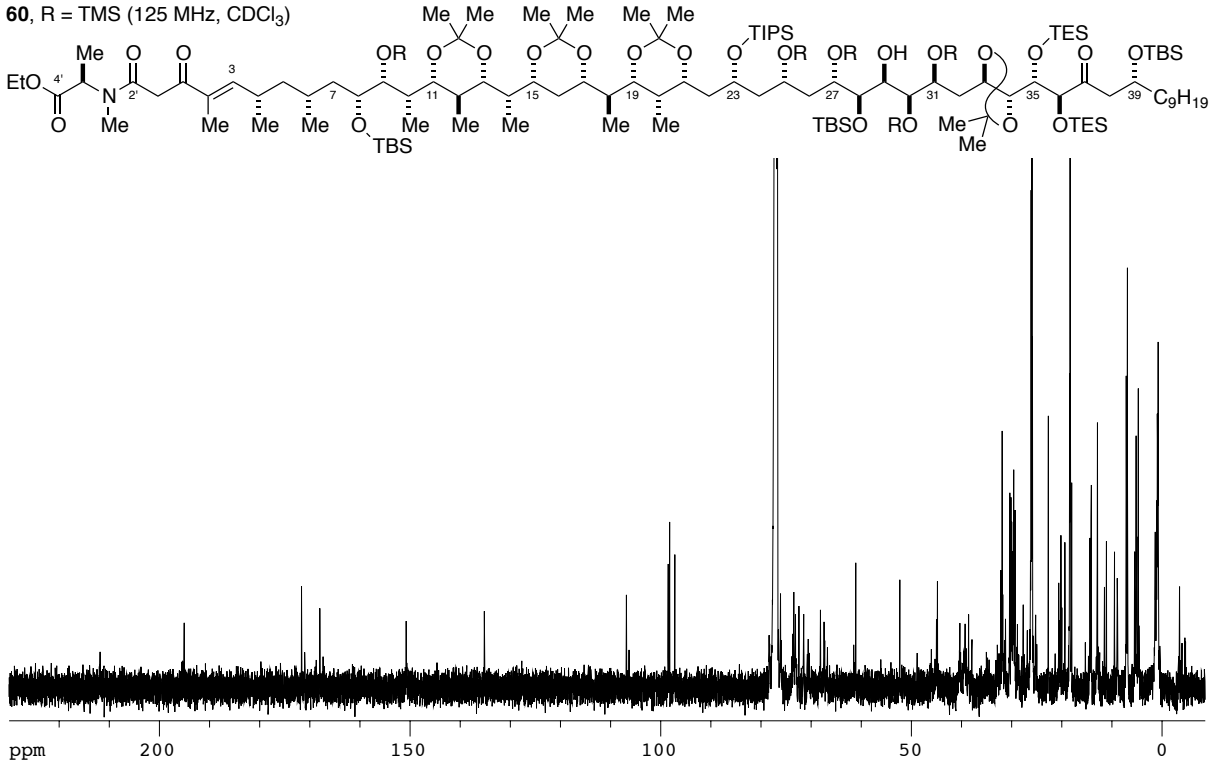

59, R = TMS
(600 MHz, CDCl3)
TIPS
TES
OTBS
TBS
TBSO
RO
OTES
C9H19
ppm
8
7
6
5
4
3
2
1
0
59, R = TMS
(125 MHz, CDCl3)
200
150
100
50
0

Compound 60.

60, R = TMS (600 MHz, $CDCl_3$)

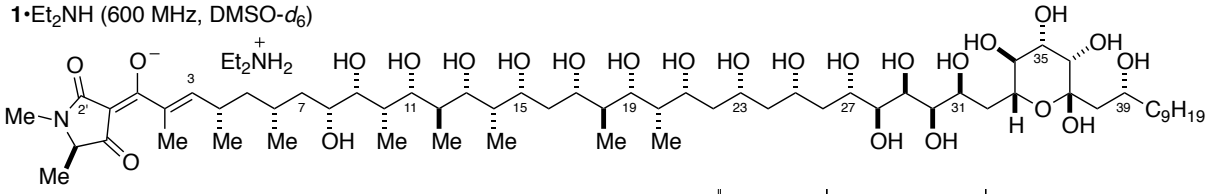


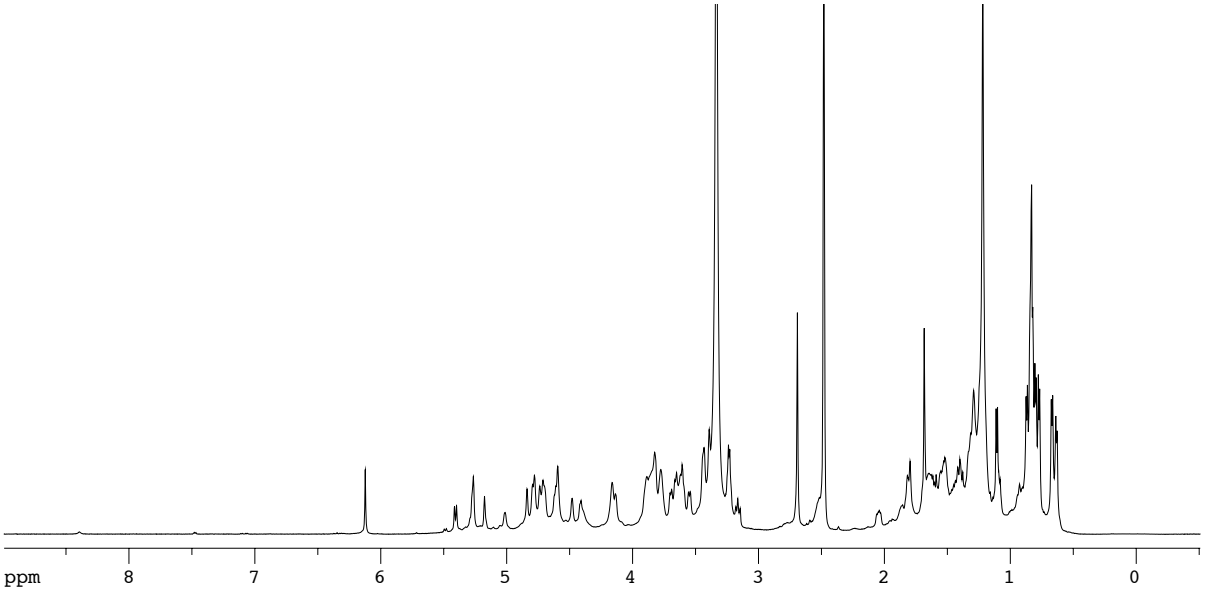
60, R = TMS (125 MHz, $CDCl_3$)



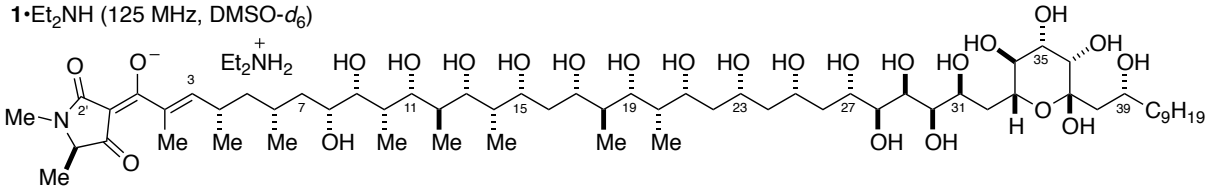
Compound 1•Et_2NH.

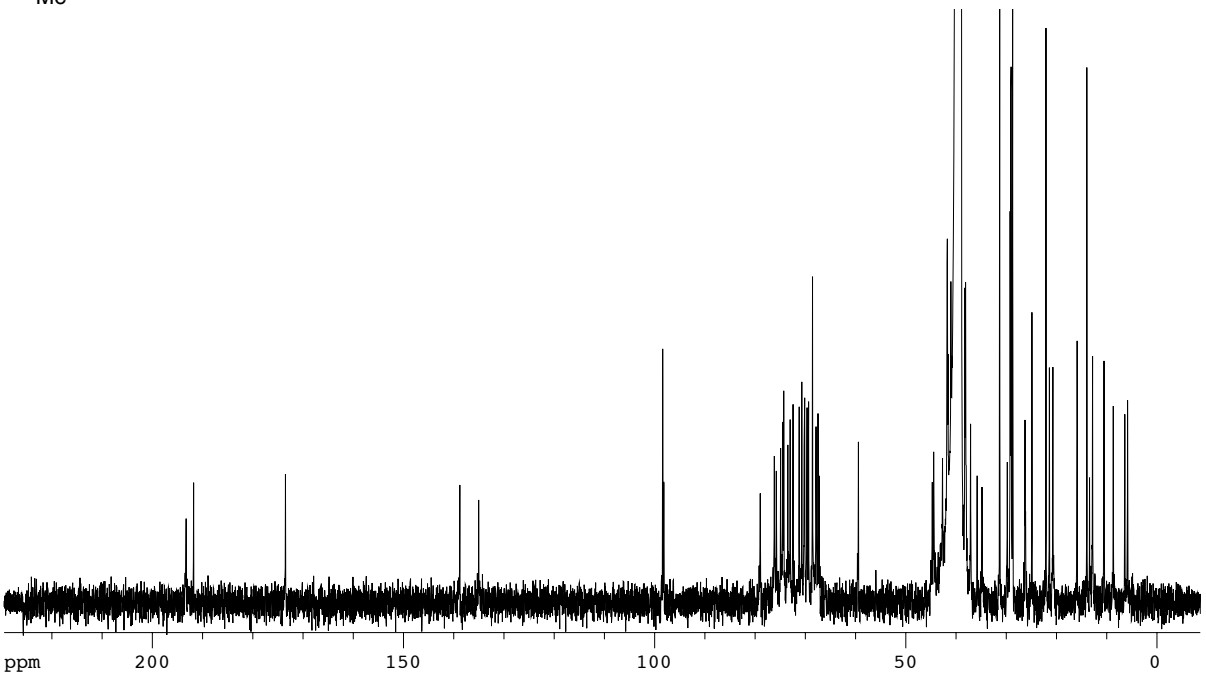
1•Et_2NH (600 MHz, DMSO-d_6)





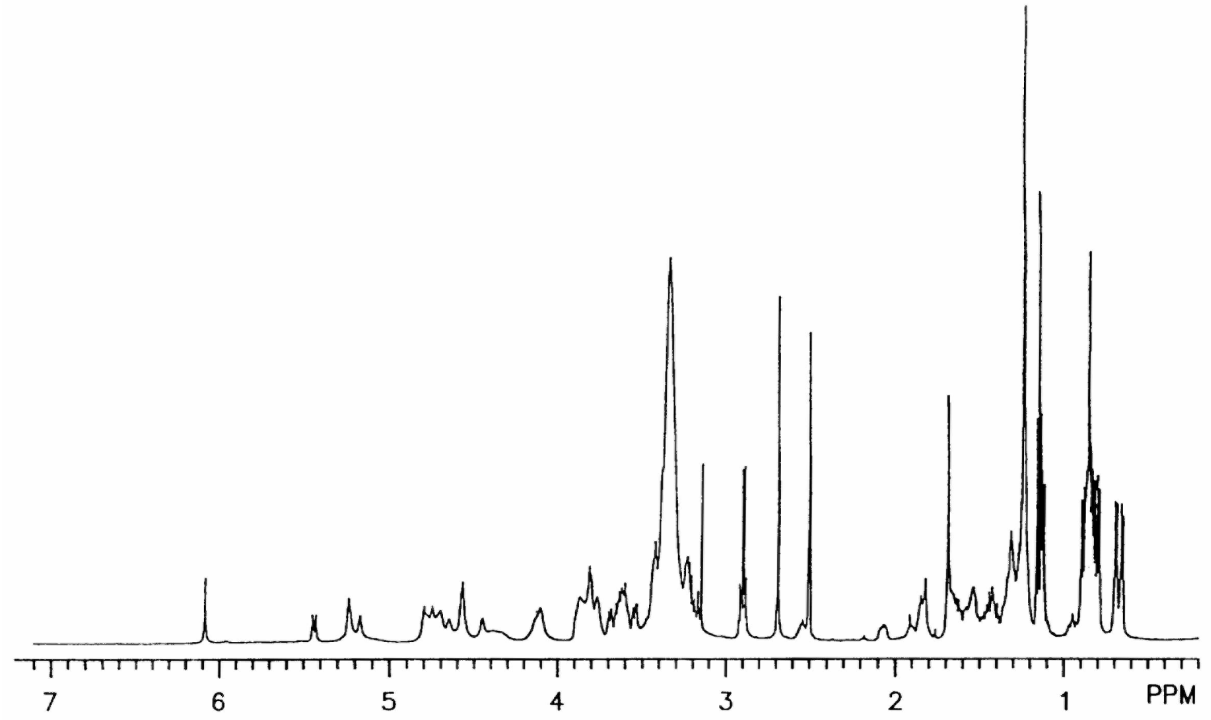
1•Et_2NH (125 MHz, DMSO-d_6)



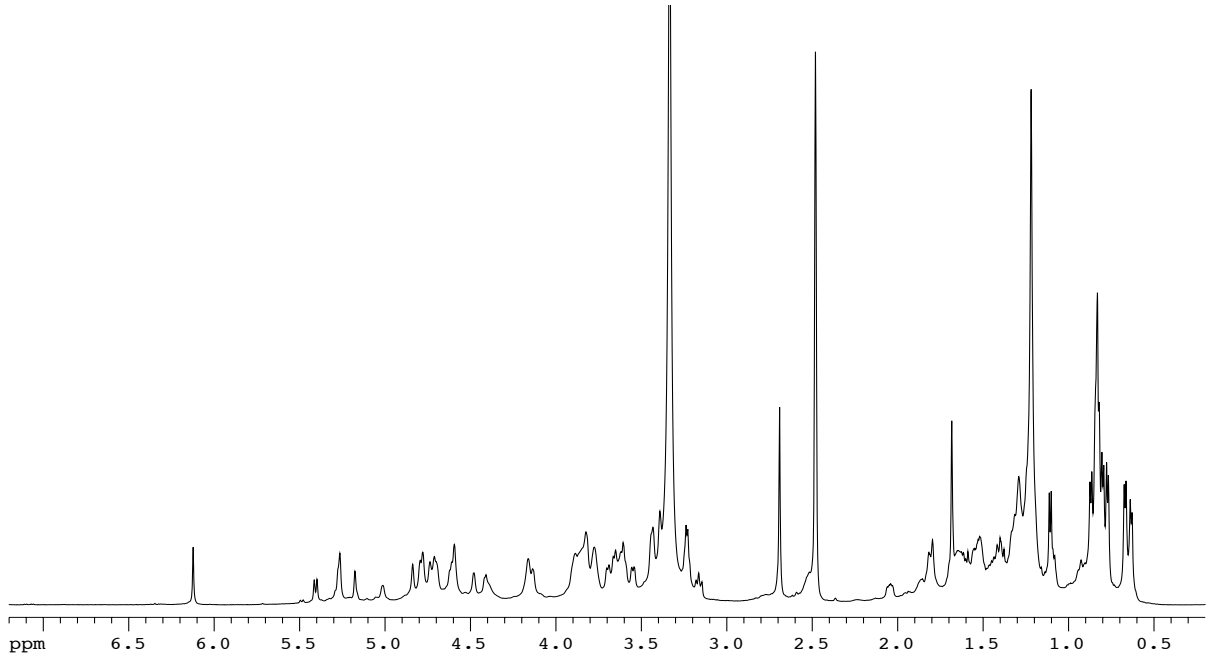


Comparison of the ^{1}H-NMR Spectrum Reported for 1•Et_2NH[a] to Our Spectrum.

Sakuda **1**•Et_2NH (500 MHz, DMSO-d_6)



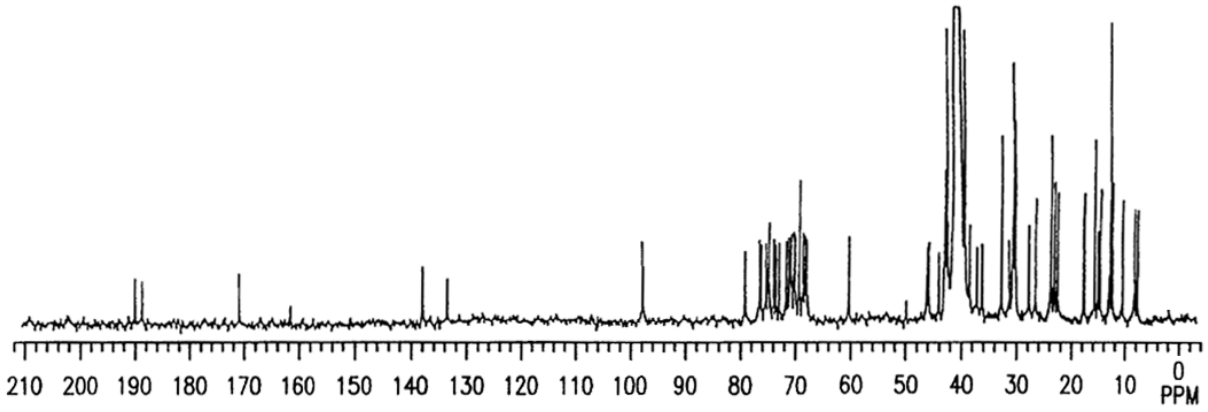
Evans **1**•Et_2NH (500 MHz, DMSO-d_6)



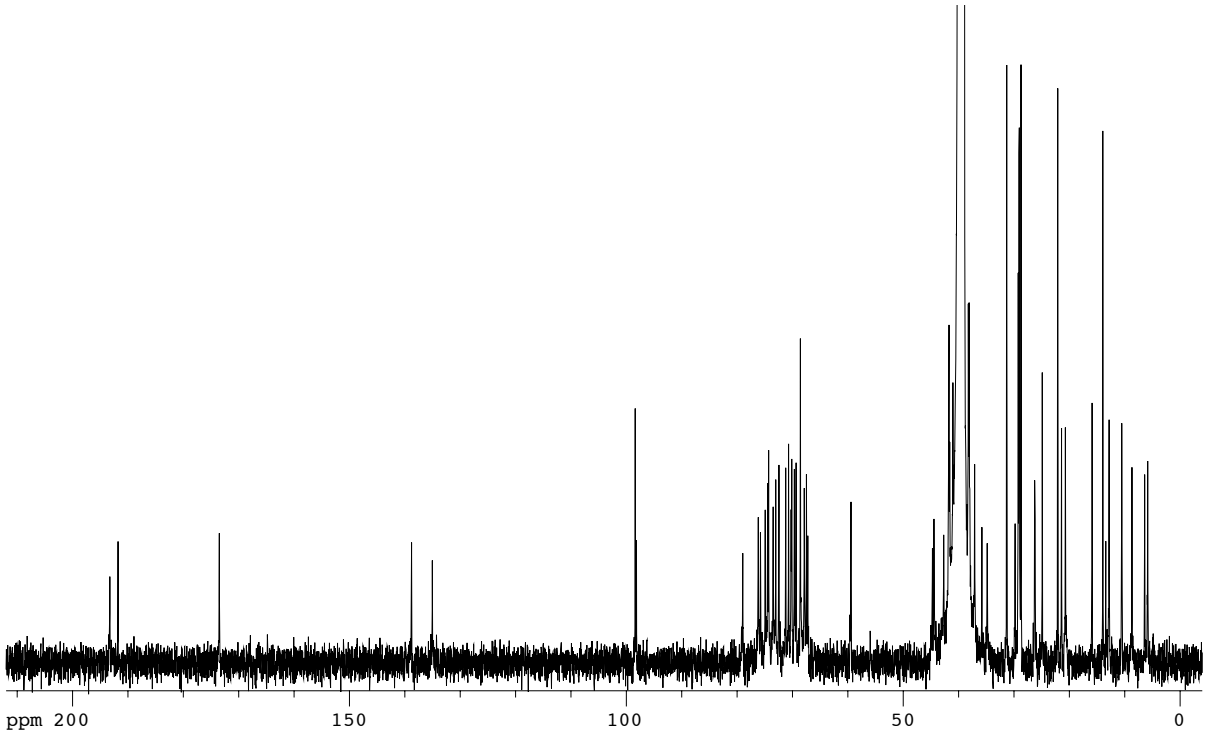
[a] Reproduced from: (a) Ono, M.; Sakuda, S.; Suzuki, A.; Isogai, A. *J. Antibiotics* **1997**, *50*, 111–118; (b) Ono, M.; Suzuki, A.; Isogai, A.; Sakuda, S. Production Aflastatin A from *Streptomyces* sp., A Pharmaceutical Composition and Methods of Use. U.S. Patent 5,773,263, June 30, 1998.

Comparison of the ^{13}C-NMR Spectrum Reported for 1•Et_2NH[a] to Our Spectrum.

Sakuda **1**•Et_2NH (125 MHz, DMSO-d_6)



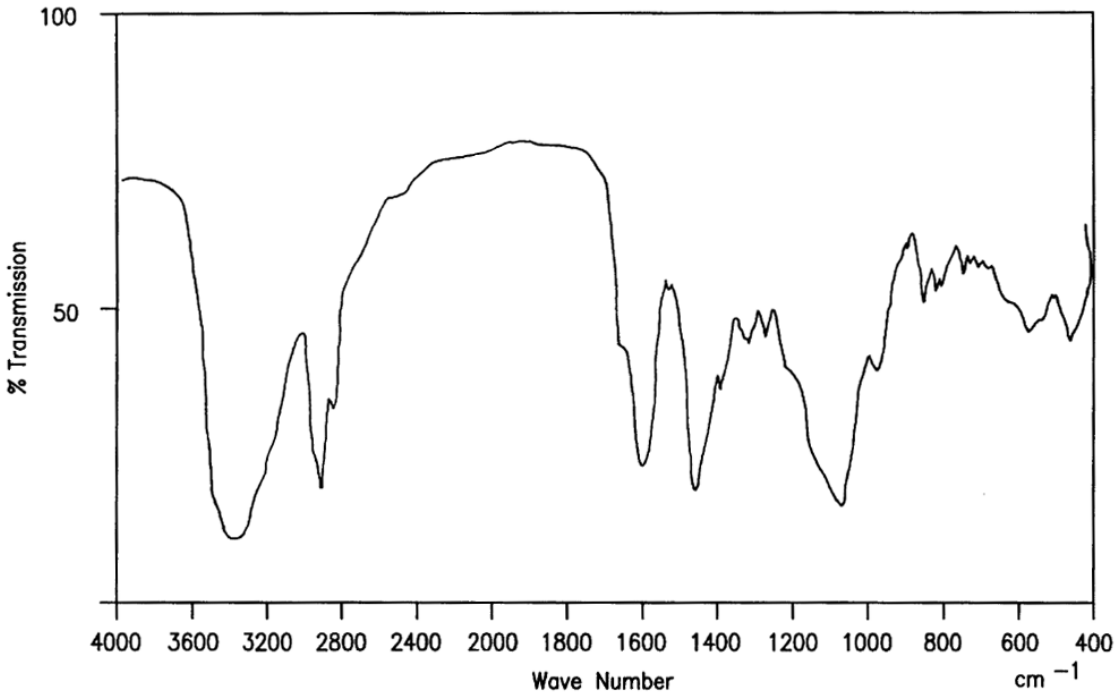
Evans **1**•Et_2NH (125 MHz, DMSO-d_6)



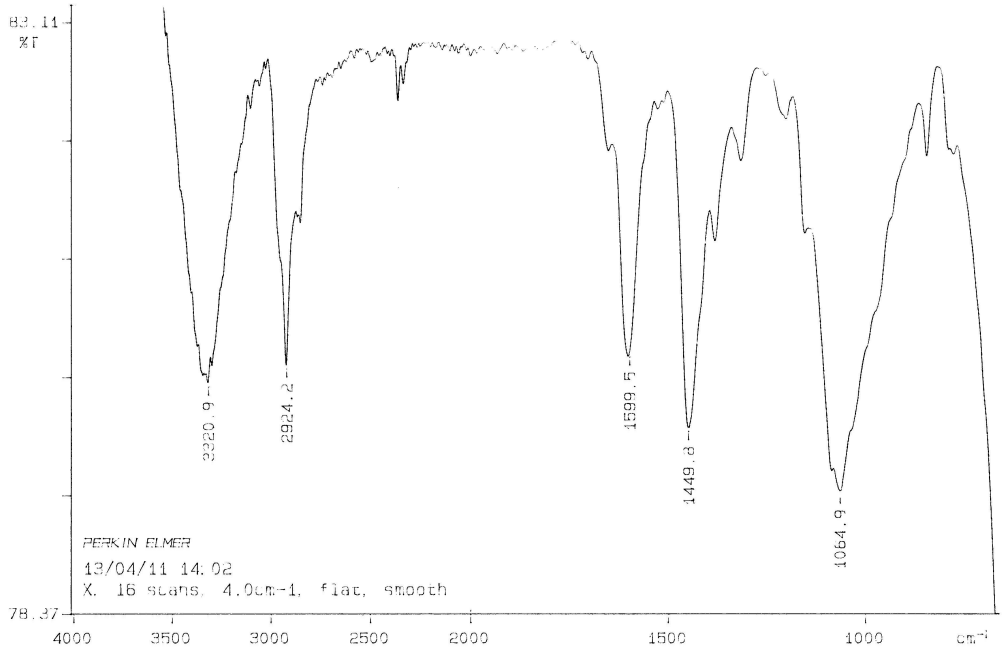
[a] Reproduced from: (a) Ono, M.; Sakuda, S.; Suzuki, A.; Isogai, A. *J. Antibiotics* **1997**, *50*, 111–118; (b) Ono, M.; Suzuki, A.; Isogai, A.; Sakuda, S. Production Aflastatin A from *Streptomyces* sp., A Pharmaceutical Composition and Methods of Use. U.S. Patent 5,773,263, June 30, 1998.

Comparison of the IR Spectrum Reported for 1•Et_2NH[a] to Our Spectrum.

Sakuda **1**•Et_2NH (KBr)



Evans **1**•Et_2NH (NaCl)



[a] Reproduced from: (a) Ono, M.; Sakuda, S.; Suzuki, A.; Isogai, A. *J. Antibiotics* **1997**, *50*, 111–118; (b) Ono, M.; Suzuki, A.; Isogai, A.; Sakuda, S. Production Aflastatin A from *Streptomyces* sp., A Pharmaceutical Composition and Methods of Use. U.S. Patent 5,773,263, June 30, 1998.